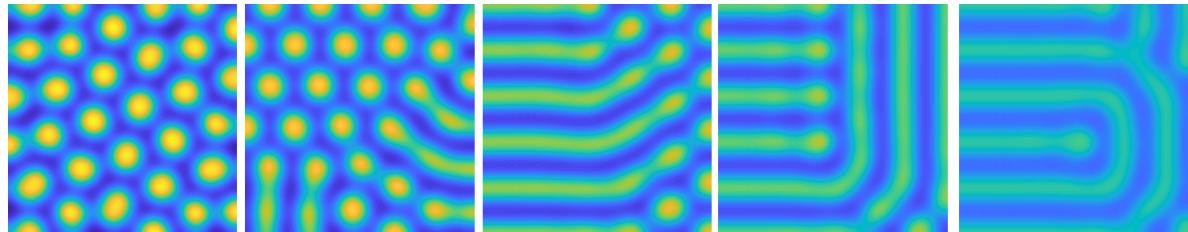


Mathematical Biology



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Based on the notes of Prof. Eamonn A. Gaffney (University of Oxford)

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Chapter 1

Introduction

This course builds directly on the techniques you may have learned in MA0232 Modelling with Differential Equations. As in MA0232 we will develop techniques that allow us to model biological phenomena and, in particular, derive properties of the equations without explicitly solving them.

This may seem counter-intuitive as we have a variety of techniques that enable us to solve many of the equations that we see in closed form. Further, numerical simulations can be used to illustrate equations that we cannot solve analytically. However, even when direct solutions are available, they may not always enable clear interpretations and understanding of the underlying system. Equally, our analytical techniques will give us confidence in the solutions produced by numerical software.

Initially, we will focus on systems where the dynamics are spatially homogeneous. In other words the interactions are occurring uniformly across space, the agents we are modelling are '*well mixed*' and we only need to consider the evolution of the agent populations over time. Such dynamics are typically modelled (but not exclusively, as we will see in Chapter 4) using ordinary differential equations, ODEs.

We will then proceed to consider systems where there is explicit spatial variation. In ecological and biological contexts the main physical phenomenon governing the spatial movement of agents is typically (but again not exclusively), diffusion. Diffusion, as we will see in Chapter 4 models random movement, thus, we are generally assuming that our agents do not have a preferred movement direction.

However, before we investigate such interesting cases as animal pigmentation patterning and neural pulses we must begin at the start with the techniques you should have already covered.

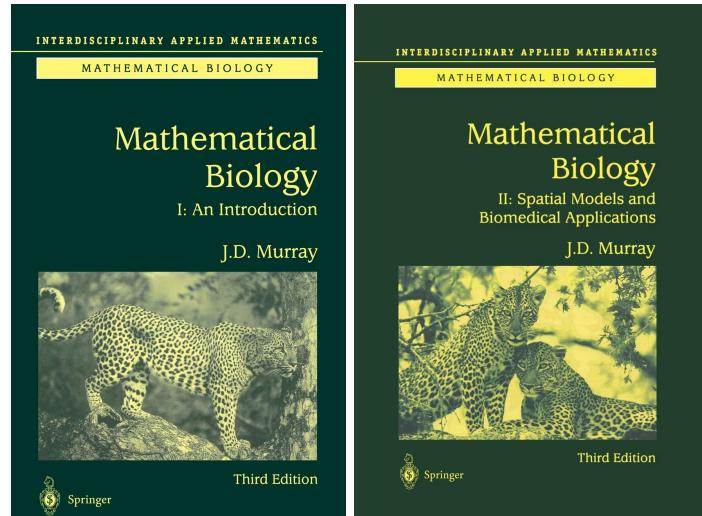
1.1 References

The main references for this lecture course will be:

- J. D. Murray, Mathematical Biology, 3rd edition, Volume I.
- J. D. Murray, Mathematical Biology, 3rd edition, Volume II.

Other useful references include:

- J. P. Keener and J. Sneyd, Mathematical Physiology.
- L. Edelstein-Keshet, Mathematical Models in Biology.
- N. F. Britton, Essential Mathematical Biology.



(a)

(b)



(c)

Figure 1.1: (a), (b) The bibles of Mathematical Biology. (c) Prof. Jim D. Murray (right), Prof. Philip K. Maini (centre) and Dr Thomas E. Woolley (left).

Chapter 2

Things you have forgotten

Whilst we are considering spatially uniform dynamics we will be concerned with ordinary differential equations, ODEs.

Definition 1. *An ordinary differential equation (ODE) is a differential equation containing one or more functions of exactly one independent variable and its derivatives.*

We will be considering the rate of change of a variable, u , with respect to another variable, t , normally time. This dependence will be denoted

$$u(t). \quad (2.1)$$

Here, u is a scalar function (*i.e.* one-dimensional), but more generally, we will be considering systems of variables

$$\mathbf{u}(t) = (u_1(t), u_2(t), \dots, u_k(t)). \quad (2.2)$$

The values of u or \mathbf{u} define quantities of interest. For example they could be an animal population density, or biochemical concentrations. On the board we will usually write bold symbols with an underline¹ as it is easier to see, thus, $\mathbf{u} = \underline{\mathbf{u}}$.

In order to link the changes in these quantities we define a system of ODEs in the most general way possible,

$$\mathbf{F}\left(t, \mathbf{u}, \frac{d\mathbf{u}}{dt}, \frac{d^2\mathbf{u}}{dt^2}, \dots, \frac{d^n\mathbf{u}}{dt^n}\right) = 0, \quad (2.3)$$

with initial condition given by

$$\mathbf{u}(0) = \mathbf{u}_0. \quad (2.4)$$

Note that the initial condition is kept general as we will usually be interested in how the dynamics of the system change for different starting points.

Definition 2. *A system of differential equations is **autonomous** if the system does not explicitly depend on the independent variable.*

When the variable is time, they are also called time-invariant systems, this simply means that we are assuming that the defined underlying laws of the system are identical to those for any point in the past, or future.

Definition 3. *To save time we use a dot or prime mark to denote a derivative with respect to the argument, thus,*

$$\dot{\mathbf{u}}(t) = \mathbf{u}'(t) = \frac{d\mathbf{u}}{dt}. \quad (2.5)$$

¹I was once told that we use underlines to illustrate bold variables because when typesetting a document an underline would tell the printer that that symbol needed to be bold. However, if this is true, how did the writer indicate that they wanted a symbol underlined?

Traditionally, dots are primarily used when the variable is time and primes are used otherwise. Note that higher orders derivatives are signified by the appropriate number of dots or primes. Namely, a second derivative would be denoted by two dots or primes, etc.

In this course we are going to occupy ourselves with systems of autonomous first order equations, of the form

$$\frac{du}{dt} = \dot{u} = \mathbf{F}(u). \quad (2.6)$$

This may seem highly restrictive. However, systems of first order equations can have extremely complicated properties, such as oscillations and chaos, which we will try to understand.

2.1 How to model a system

Modelling a system, whether it be physical, chemical, or biological, is, in some ways, more of an art than a science. You try and strip away all extraneous information and mathematically describe that which is left. In physics there are physical laws to help you, *e.g.* gravity, conservation of energy and mass. Unfortunately, biology has no such fundamental laws. Thus, we must use experimental intuition, *e.g.* predator-prey interactions from population data. Critically, the modelling should always form part of a cyclical process (see Figure 2.1).

You try to start with physical intuition (experiment), represent the important parts mathematically (model), hopefully reproduce reality (test) and, finally, use your mathematical model to predict unknown outcomes (predict). These predictions can then feed back into experiment and the process begins anew.

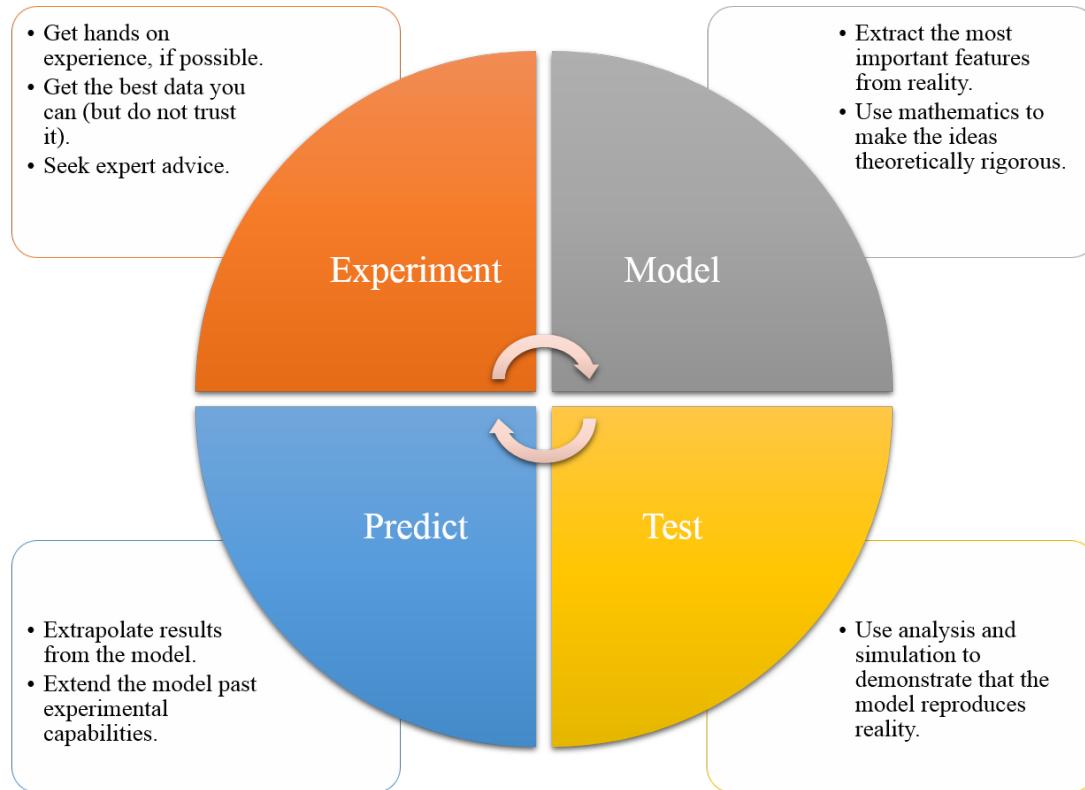


Figure 2.1: Diagram of the modelling cycle.

2.2 Law of Mass Action

In this section we will learn about a very general technique that will allow us to build an ODE system out of multiple interacting populations. These populations could represent chemical compounds, humans, cells or animals as well as different states within a population *i.e.* infected humans and susceptible humans. The law presented in this section is applied whenever the populations of the system are able to: (i) change identities; (ii) create more population members; or (iii) cause populations to decay. Specific examples of each of these interactions are, respectively: (i) susceptible humans becoming infected through interactions with a diseased person; (ii) animals giving birth; (iii) predators eating prey. Note that a change-of-identity interaction can itself be thought as a combination of creation and degradation operations. For example, in the above case of infection a member of the susceptible human population is removed from the system, whilst an infected human is added to the system. Thus, all interactions can be made through combining creation and degradation operations.

We use chemical reaction notation to specify the outcomes of population interactions. Consider a system composed of n different interacting populations (u_1, \dots, u_n) . We assume that all interactions between the population elements lead to the creation, or destruction, of one (or more) of the n populations.

Definition 4. A **rate equation** specifies that an interaction involves a_1 members of population u_1 , a_2 members of population u_2 , etc. and produces b_1 members of population u_1 , b_2 members of population u_2 , etc. The equation is written as

$$a_1 u_1 + a_2 u_2 + \dots + a_n u_n \xrightarrow{r} b_1 u_1 + b_2 u_2 + \dots + b_n u_n, \quad (2.7)$$

where $r > 0$ is the **reaction rate**.

Note that some of the a_i and b_i values can be zero.

Rate equations provide a rigorous way of defining all of the interactions a system is assumed to undergo. However, we still require a method of converting the rate equation into an ODE. This is the power of the Law of Mass Action.

Definition 5. The **Law of Mass Action** states that production rate of a reaction is directly proportional to the product of the input population sizes. Specifically, if

$$a_1 u_1 + a_2 u_2 + \dots + a_n u_n \xrightarrow{r} b_1 u_1 + b_2 u_2 + \dots + b_n u_n$$

is the reaction of interest then the production rate is proportional to

$$r u_1^{a_1} u_2^{a_2} \dots u_n^{a_n} \quad (2.8)$$

and the accompanying ODEs are

$$\dot{u}_1 = (b_1 - a_1) r u_1^{a_1} u_2^{a_2} \dots u_n^{a_n}, \quad (2.9)$$

$$\dot{u}_2 = (b_2 - a_2) r u_1^{a_1} u_2^{a_2} \dots u_n^{a_n}, \quad (2.10)$$

$$\vdots \quad (2.11)$$

$$\dot{u}_n = (b_n - a_n) r u_1^{a_1} u_2^{a_2} \dots u_n^{a_n}. \quad (2.12)$$

Note that in converting from reaction equation to the ODE of u_i we to account for the stoichiometry, *i.e.* $(a_i - b_i)$. Further, when multiple reactions are considered, the terms arising from the Law of Mass Action are simply added together as independent terms.

Example 2.2.1 Creating logistic growth

Consider a bacterial population u and a nutrient population v , such that the bacteria uses the nutrient to reproduce, *i.e.* ,

$$u + v \xrightarrow{R} 2u,$$

and the initial conditions are $u(0) = u_0$ and $v(0) = v_0$.

2.3 Non-dimensionalisation

To non-dimensionalise a system of equations, we have the following rules:

1. Identify all the variables;
2. Replace each variable with a quantity scaled relative to a characteristic unit of measure (to be determined);
3. Choose the definition of the characteristic unit for each variable;
4. Rewrite the system of equations in terms of the new dimensionless quantities.

We note three particular points about these rules. Firstly, the theory behind non-dimensionalisation is straight forward. Namely, we substitute scaled variables into an equation system and massage the equations until we have rearranged the system to produce the desired outcome. However, in practice the difficulty of the technique lies in the algebraic manipulation; it is very easy for the terms to become lost during the manipulation. Thus, care must be taken during the algebraic manipulation stage.

Secondly, you will notice the word ‘choose’ in point 3. This means that it possible to construct many different non-dimensionalised systems from the same system of equations, *i.e.* non-dimensionalisation is non-unique. We usually choose the characteristic unit of each variable to either emphasise one of the terms in a system or to remove as many parameters as possible.

Finally, this technique is hard to demonstrate in generality. It is much better to consider a number of examples and see how the technique works in action. Thus, what follows will be a select number of examples, which along with your problem sheets should give you a good basis in the theory. However, do not think that these are all the examples you could face.

It should be noted that there is little consistency in nomenclature across book when considering the separation of variables into their dimensional and non-dimensional components. Thus, always be clear in your definitions.

2.3.1 Examples of non-dimensionalisation through substitution of variables

Example 2.3.2 Substituting variables

Consider the equation for logistic growth,

$$\dot{u} = ru \left(1 - \frac{u}{K}\right), \quad u(0) = u_0. \quad (2.17)$$

2.3.2 Examples of non-dimensionalisation through the arrow method

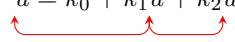
The substitution method shown in Section 2.3.1 will always work, assuming that the algebra is manipulated correctly. However, the method can be cumbersome and slow. Moreover, because it involves lots of algebraic manipulations there are many chances to make a mistake.

An alternative method rests on using arrows to identify the desired balances. This can be much quicker as the initial stages do not require laborious substitution. However, we have to be more careful because not all balances that we can ‘draw’ using the arrows will be valid.

The idea behind the arrow method is that you draw arrows between the quantities that are going to ‘balance’, which simply means they are going to have the same coefficient in the final non-dimensionalised form. The process is generally the same as the substitution method. However, we must remember that in order to specify the problem completely the number of valid arrow balances must equal the number of variables. For example, if a problem depends on u and t we would need two balances. Alternatively, if the problem depended on u , v , and t we would need three valid balances.

Example 2.3.3 Arrow method

Consider the following equation

$$\dot{u} = k_0 + k_1 u + k_2 u^2, \quad u(0) = u_0. \quad (2.18)$$


2.4 Stationary states and stability

Now that we are able to model and simplify a physical system, we want to predict what the equations will do without having to simulate the system each time. Specifically, we are not interested in the transient initial behaviour of the equations, we want to understand what the trajectories will like look far into the future. To enable us to generate insights we first need two important definitions.

Definition 6. A state, \mathbf{u}_s , is a **steady state** or **stationary state** of the ODE system

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}) \quad (2.20)$$

if it satisfies $\mathbf{F}(\mathbf{u}_s) = 0$.

This definition simply states that if the ODE system ever reaches \mathbf{u}_s then the system will not evolve further because all of the dynamics are in equilibrium. This is a useful concept, but currently incomplete.

For example, you can (theoretically) stand a pencil on its tip and it would remain stationary, if it were not perturbed (see Figure 2.2). Hence, this is a stationary state orientation of the pencil. However, it would require only a very small perturbation to cause the pencil to fall over and, thus, transition from the state of being on its point to being on its side (see Figure 2.2). Given a large enough perturbation (*i.e.* picking the pencil up) you could reset the pencil to the previous state of standing on its point. However, it requires a larger perturbation to reset the pencil than it does to knock it over and, so, we see that although these state are both stationary states they are somehow fundamentally different. This difference comes down to the intuitive concept of ‘stability’.

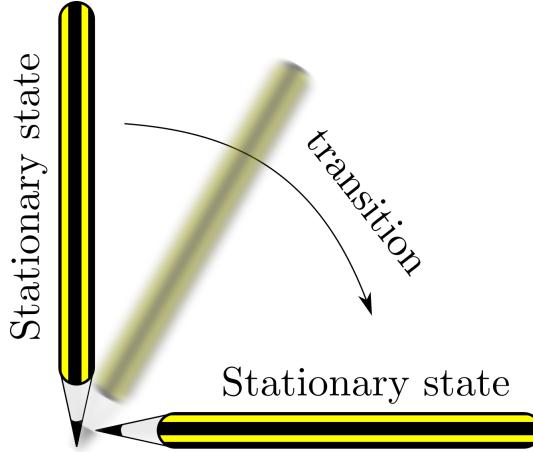


Figure 2.2: Stationary states of a pencil.

Definition 7. A steady state, \mathbf{u}_s , of the ODE system

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}) \quad (2.21)$$

is **stable** if for all $\epsilon > 0$, there exists a $\delta > 0$ and a $t_0 > 0$ such that whenever $|\mathbf{u}(t) - \mathbf{u}_s| < \delta$ then $|\mathbf{u}(t) - \mathbf{u}_s| < \epsilon$ for all $t \geq t_0$. Otherwise the steady state is **unstable**

Simply put, this means that a state, \mathbf{u}_s , is stable if whenever a solution $\mathbf{u}(t)$ comes close enough to it then the solution tends to the state i.e. $\mathbf{u}(t) \rightarrow \mathbf{u}_s$. In the example of the pencil, both the vertical and horizontal orientations of the pencil are stationary states. However, only the horizontal orientation is stable.

2.5 Linear stability

Having a definition of stability is one thing, but we need a method of characterising whether a system is stable or unstable. The crux of this characterisation is to consider the dynamics of an ODE system near its stationary points. To do this we substitute a solution into the equations that is a perturbation about the steady state. Using Taylor series we expand the system in terms of the perturbation and keep only the linear terms as we are assuming that the perturbation is small. Since the system is now linear we can solve the approximate equations completely and, thus, they will tell us what dynamics to expect close to the steady states.

Theorem 2.5.1. Suppose u_s is a steady state of the one dimensional ODE,

$$\dot{u} = F(u), \quad (2.22)$$

then u_s is linearly stable if $dF(u_s)/du < 0$ and linearly unstable if $dF(u_s)/du > 0$.

Proof. The proof can be found in Appendix A. □

We make a number of remarks about the theorem's statement:

- The theorem makes no claim about the solutions properties in the case that the first derivative $dF(u_s)/du = 0$. In this specific case we would have to go to higher order in the Taylor expansion.

- Linear stability only tells us what happens close to the steady state. Thus, although a state may be stable, we have no metric for how close we have to be to the steady state before we are attracted to the stable point.
- In the case that u_s is unstable we cannot conclude what happens to the trajectory. Indeed, a trajectory near an unstable point may grow without bound or, simply tend to one of the other stationary states in the system that is stable.

Example 2.5.4 Stationary states and stability of the logistic equation

The non-dimensionalised logistic equation is (as we have seen before)

$$\dot{u} = u(1 - u). \quad (2.23)$$

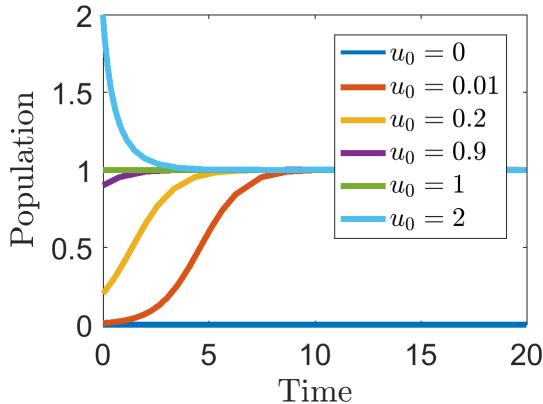


Figure 2.3: Multiple simulations of equation (2.23) with different initial conditions, u_0 , (noted in the legend), illustrating the stationary states and their stability characteristics.

In the case that we have a system of ODEs, we note that the definition of a steady state immediately generalises to any number of variables. Specifically, if we have n variables, $\mathbf{u} = (u_1, \dots, u_n)$ then there must be n ODEs, $\mathbf{F}(\mathbf{u}) = (F_1(u_1, \dots, u_n), \dots, F_n(u_1, \dots, u_n))$, one for each variable, in order for the system to be uniquely defined. Thus, the steady states, \mathbf{u}_s , are found from solving $\mathbf{F}(\mathbf{u}_s) = 0$. The derivation of linear stability also extends to higher similarly, however, we need to first define the Jacobian.

Definition 8. *The Jacobian, \mathbf{J} , of an ODE system,*

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}), \quad (2.26)$$

is the matrix of partial derivatives of each function, with respect to each argument,

$$\mathbf{J} = \left[\frac{\partial F_i}{\partial u_j} \right]_{i,j=1,\dots,n} = \begin{bmatrix} \frac{\partial F_1}{\partial u_1} & \frac{\partial F_1}{\partial u_2} & \cdots & \frac{\partial F_1}{\partial u_n} \\ \frac{\partial F_2}{\partial u_1} & \frac{\partial F_2}{\partial u_2} & \cdots & \frac{\partial F_2}{\partial u_n} \\ \vdots & \ddots & \ddots & \vdots \\ \frac{\partial F_n}{\partial u_1} & \frac{\partial F_n}{\partial u_2} & \cdots & \frac{\partial F_n}{\partial u_n} \end{bmatrix}. \quad (2.27)$$

For brevity, it is common practice to write a partial derivative as a subscript, *i.e.*

$$\frac{\partial F}{\partial u} = F_u. \quad (2.28)$$

Equally, unless otherwise specified, we assume that the Jacobian is evaluated at the steady state.

Theorem 2.5.2. Suppose \mathbf{u}_s is a steady state of the ODE system

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}), \quad (2.29)$$

where \mathbf{F} is continuously differentiable everywhere in all of its arguments and the Jacobian is locally invertible. The linear stability of \mathbf{u}_s will depend on the eigenvalues of the Jacobian. Namely:

- if all eigenvalues have negative real part then the steady state is stable;
- if any eigenvalue has positive real part then the steady state is unstable.

In systems of two species we can be more specific and split the cases up further. Namely, suppose the steady state has eigenvalues λ_1 and λ_2 ,

	Eigenvalue characteristic	Steady state characteristic
Eigenvalues are real	$\lambda_1 \geq \lambda_2 > 0$	Unstable node
	$\lambda_1 > 0 > \lambda_2$	Saddle point
	$0 > \lambda_1 \geq \lambda_2$	Stable node
Eigenvalues are imaginary	$\text{Re}(\lambda_1) \geq \text{Re}(\lambda_2) > 0$	Unstable spiral
	$\text{Re}(\lambda_1) = \text{Re}(\lambda_2) = 0$	Centre node
	$\text{Re}(\lambda_1) \leq \text{Re}(\lambda_2) < 0$	Stable spiral

Proof. The proofs for general systems can be found in Appendix B and the specific proof for two species systems can be found in Appendix C. \square

Definition 9. A bifurcation point of a system is a parameter value at which the characteristics of the steady states change. This can be either in number of steady states, or their stability.

Example 2.5.5 Schnakenberg kinetics

Calculate the steady state of the following system of equations

$$\dot{u} = f(u, v) = -u + u^2v, \quad (2.30)$$

$$\dot{v} = g(u, v) = \beta - u^2v, \quad (2.31)$$

and characterise its stability.

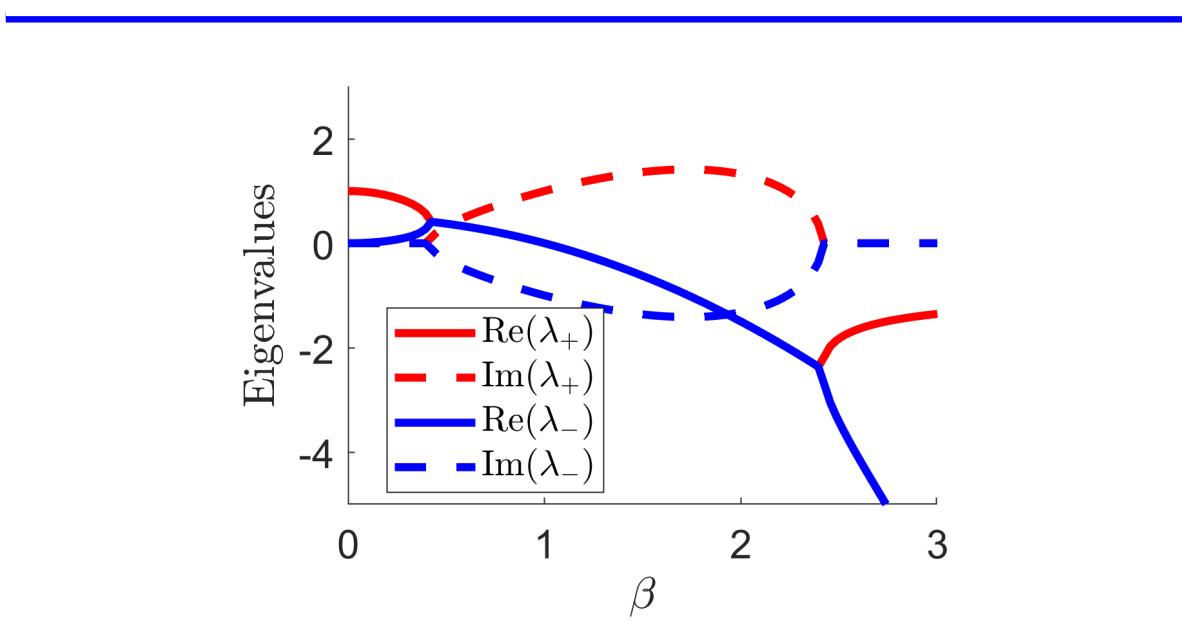


Figure 2.4: Plotting the eigenvalues from example 2.5.5.

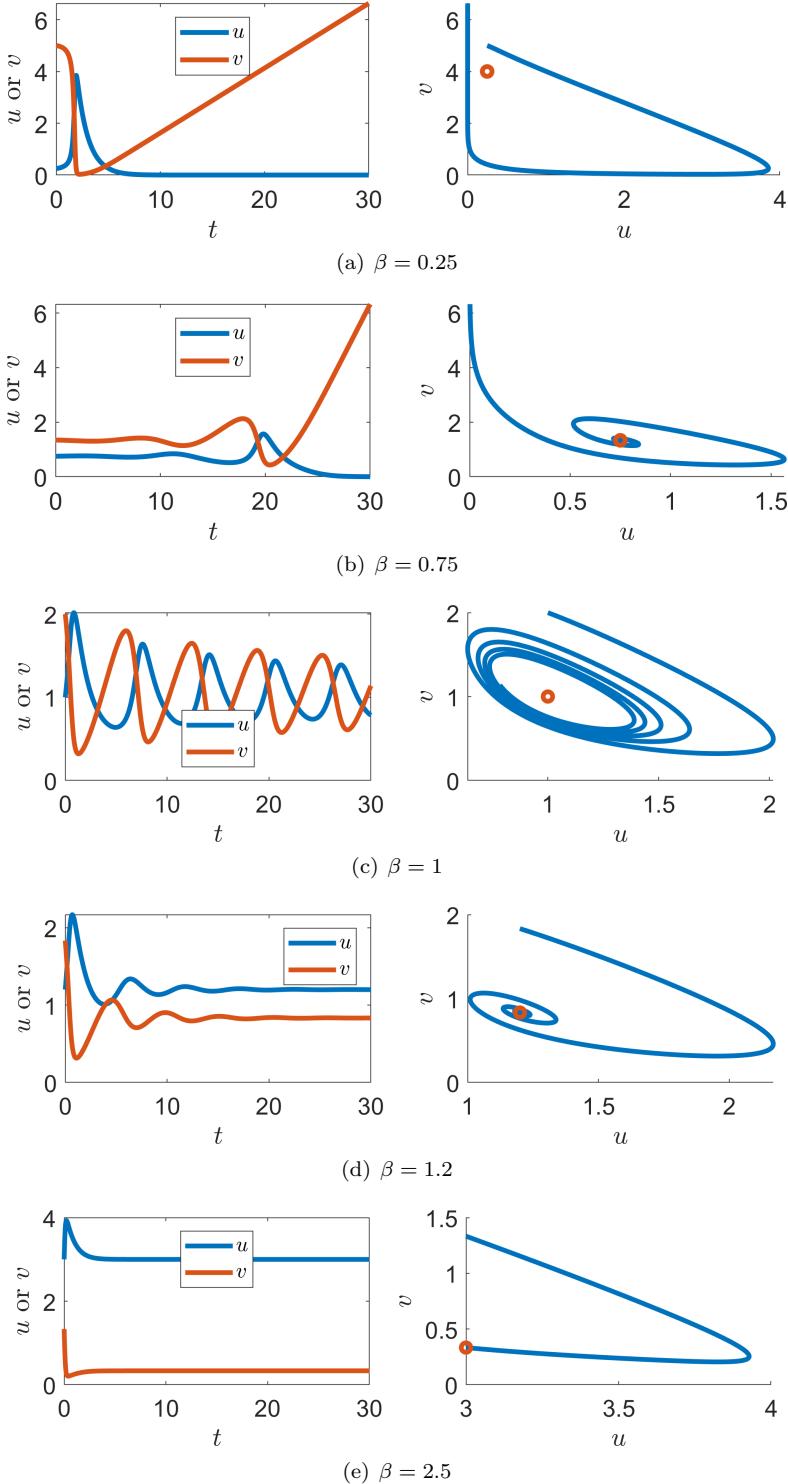


Figure 2.5: Illustrating the stationary states and stability characteristics of the Schnakenberg equations from example 2.5.5. The left plots show the trajectories of each population over time. The right plots show the corresponding phase planes. The red circle in each case is the steady state $(\beta, 1/\beta)$, where β is noted beneath each figure.

2.6 Curve sketching

Algebraic and analytical solutions will always be the surest way of providing an answer, as they provide all information regarding the quantitative values and parameter dependencies. However, such solutions are not always possible. Sometimes the algebra is not tractable, or the solution might be too cumbersome to provide clear insight. Thus, we often fall back on the skill of curve sketching.

There is no defined process to curve sketching. Essentially, you are looking for simple features that you understand and, thus, the best approach to curve sketching is through gaining experience. Namely, the more functions you sketch the larger your catalogue of known shapes. However, there are some general tips that will help you sketch simple curves, as well as a number of stereotypical examples you should know well.

Suppose we want to sketch the curve $f(x, \mu)$, where x is the argument and μ is a parameter, the general tips are:

- look for any “obvious” roots, x_c such that $f(x_c) = 0$ of the function you are trying *i.e.* consider $0, 1, \infty$, or immediate simple parameter dependencies, *e.g.* $x_c = \mu$, or μ^2 .
- consider the general curve properties, thus, even if you cannot derive the roots, can you say that there must be roots? For example a cubic must always have at least one real root.
- for any roots that you have found consider the derivative close to the points (if possible). This will tell you which way the curve is crossing the x -axis. Namely, if $f' > 0$ the curve is passing into the upper half-plane, whilst if $f' < 0$ then the curve is passing into the lower half-plane.
- consider what happens to the function near $x = 0$ and $x \rightarrow \infty$. Equally, are there any particularly simple limits of μ ?
- consider the dependency of the function of f on μ . Are there direct correlations? Namely, does increasing μ always increase/decrease the value of $f(x, \mu)$?

2.6.1 Specific curves and their properties

Generally, in this course, we will consider polynomial dependencies, as well as rational polynomial fractions. Although this seems quite restrictive, most models are constructed out of this small tool kit. Specifically, because they have “nice” properties, such as being well understood and easy to sketch. Further, even if we come across something more complicated, Taylor series guarantees that we can consider polynomial expansions in some small interval around the point of interest.

2.6.1.1 Polynomials

A polynomial over leading order n is guaranteed to have n roots over the complex plane. However, as we are applying these functions to real biological situations we, generally, only need to consider the real, positive roots. Thus, although a polynomial may have many roots (see Figure 2.6), we can guarantee that a minimum number exists. Specifically:

- polynomials with an odd leading order term are guaranteed to have at least one real root.
- polynomials with an even leading order term may have no real roots.

Note that just because there are roots, this does not mean that they are physically meaningful. Frequently, when multiple roots exist, we will invoke reality to justify the choice of only real, positive roots as we, generally, consider positive populations.

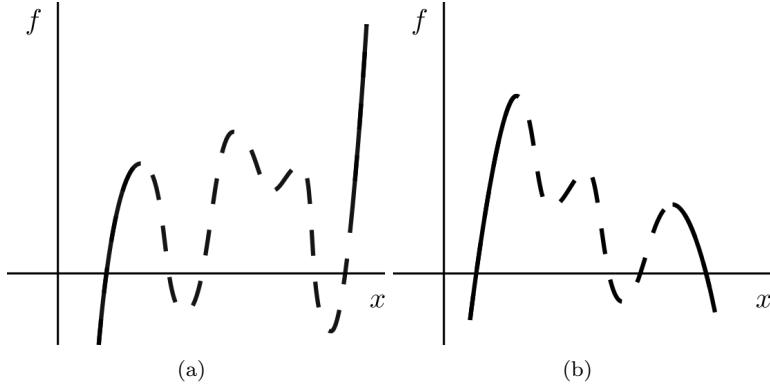


Figure 2.6: Basic polynomial properties. The lines have dashed centres as the shape can be altered depending on the specific polynomial used. However, the minimum number of roots can be guaranteed (if there are any). (a) A general odd polynomial. (b) A general even polynomial (with negative leading order term).

2.6.1.2 Hill functions

Hill functions are also common functions that are used widely as they can cover a wide variety of outcomes. They have the form

$$f(x) = \frac{\alpha x^m}{\beta^n + x^n}, \quad (2.37)$$

where α and β are control parameters.

Although, below, we consider $\alpha = \beta = 1$ changing these parameters does not, generally, change the qualitative properties we are illustrating. The parameters, only tend to influence the quantitative behaviour of the function *e.g.* how big the gradients are, or where the transitions happen.

Generally, $m = n$ (which is the usual definition of the Hill function), but there is no reason why this is so. Further, the function has different properties for the different cases of m relative to n . See Figure 2.7 for the possible outcomes. In all cases the dynamics will be dominated by x^m for small x and x^{m-n} for large x . This is why we need to consider the sign of $m - n$.

- When $m > n$, although there maybe stationary points, the curve will eventually tend to grow without bound.
- When $m = n$, $x^{m-n} = 1$. Thus, the function asymptotes to $f \rightarrow 1$. Such Hill functions are used as “switches”, namely one type of dynamic occurs when x is small and another occurs when x is large. Steepness of the switch is controlled by the size of $m = n$; larger values create a sharper transition.
- When $m < n$, $x^{m-n} = 1/x^{n-m} \rightarrow 0$ as $x \rightarrow 0$. Thus, although we have an initial hump the curve decays to zero.

Thus, we can see why Hill functions are so powerful, namely, they are able to describe growth, saturation and decay all through the sign of $m - n$.

2.7 Phase planes

2.7.1 One-dimensional

In one dimension the phase plane is a plot of the dynamics in the (u, \dot{u}) plane. Steady states can easily be read off as they are where the curve crosses the x -axis. Equally, we can determine the stability of

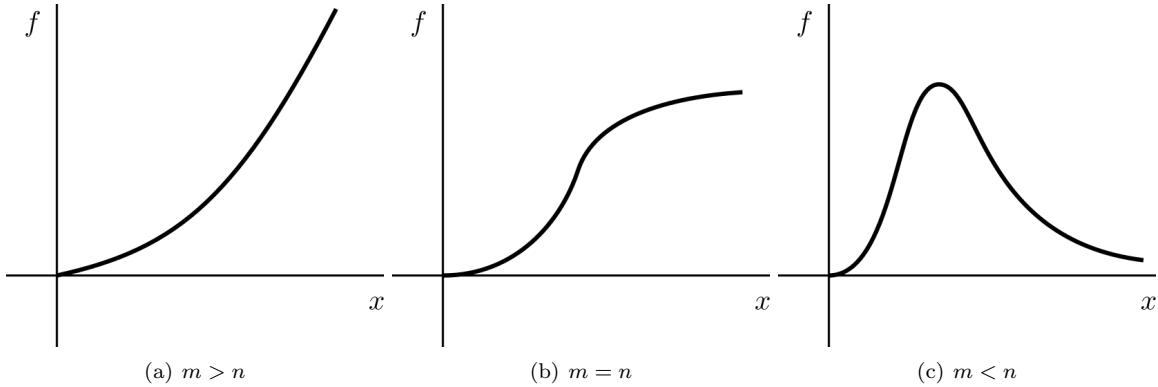


Figure 2.7: The general shape of Hill functions, equation (2.37), with (a) $m > n$, (b) $m = n$ and (c) $m < n$.

the steady states by considering where the curve lies.

Specifically, if whenever the curve lies in the top half plane $\dot{u} > 0$ and, thus, u increases over time. Thus, u will increase without bound, or until the curve crosses the x -axis, at which point $\dot{x} = 0$. Similarly, in the bottom half plane $\dot{u} < 0$ and, so, u decreases over time, either without bound, or until the curve cuts the x -axis.

Example 2.7.6 Logistic equation phase plane

Consider

$$\dot{u} = u(1 - u). \quad (2.38)$$

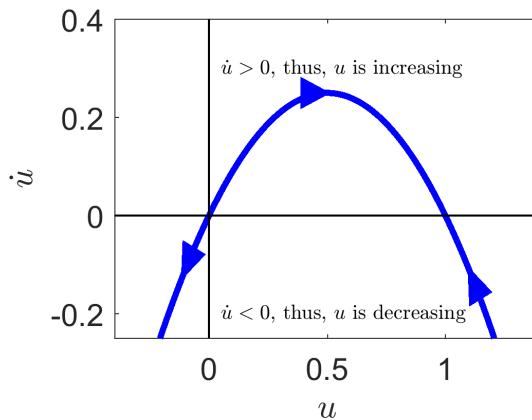


Figure 2.8: The phase plane plot of the logistic curve in (u, \dot{u}) coordinates.

2.7.2 Two-dimensional

In Section 2.7.1 we could understand the entire dynamics of a one species system in the (u, \dot{u}) plane. We would like to gain the same information for systems with multiple populations. However, when we have two variables we would have to plot four variables (u, v, \dot{u}, \dot{v}) , which is hard to visualise and almost impossible to sketch. Thus, we simplify our plot and only consider the (u, v) plane instead, which is known as the ‘phase plane’. To construct a phase plane (instead of considering a single trajectory, as in the (t, u) simulation) we consider the motion of a trajectory across all points in the (u, v) space.

To aid in our understanding we introduce a new concept.

Definition 10. Consider an ODE system

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}), \quad (2.39)$$

where $\mathbf{F}(\mathbf{u}) = (F_1(u_1, \dots, u_n), \dots, F_n(u_1, \dots, u_n))$. The nullclines are the curves defined by

$$F_i(u_1, \dots, u_n) = 0, \quad (2.40)$$

for all $i = 1, \dots, n$.

Nullclines are a useful concept because on each separate curve the dynamics of at least one variable is stationary, thus, the direction across a nullcline is simplified. Moreover, if all nullclines meet at a given point all dynamics must be stationary, *i.e.* by definition all nullclines meet at steady states.

The nullclines then delineate different dynamical regions. Namely, consider a general nullcline, for example $\dot{u} = 0$, on one side of the line $\dot{u} > 0$, whilst on the other $\dot{u} < 0$ (not this is not necessarily true). The same can be said of the $\dot{v} = 0$. Thus, the nullclines segment the (u, v) into regions of different dynamics. With this knowledge we can specify the signs of the derivatives in each region and, thus, sketch what will happen in each case.

Example 2.7.7 Two-dimensional phase plane

Consider the system

$$\dot{u} = v - (u - 2)(u - 3), \quad (2.41)$$

$$\dot{v} = v - \ln(u), \quad (2.42)$$

in the half plane $u > 0$.

]

From this example we have seen that phase planes are helpful diagrams, which encapsulate lots of stability information. However, as illustrated, in comparing the diagram with the actual analytical values of the eigenvalues it can be difficult to tell the difference between (un)stable nodes and (un)stable spirals. Equally, sketches only provide the correct insight if you draw the system correctly. If there had been a parameter in this system that we could vary then there may have been a stability case, dependent on the parameter, that we would miss if we had only drawn one diagram. Thus, a phase plane should always be backed up with linear analysis. The linear analysis provides the local information, whilst the phase plane allows us to approximately see how all the dynamics fit together.

2.8 Check list

By the end of this chapter you should be able to:

- reproduce all definitions;
- convert a system of population interactions into reaction equations;
- convert reaction equations into ODEs using the Law of Mass Action;

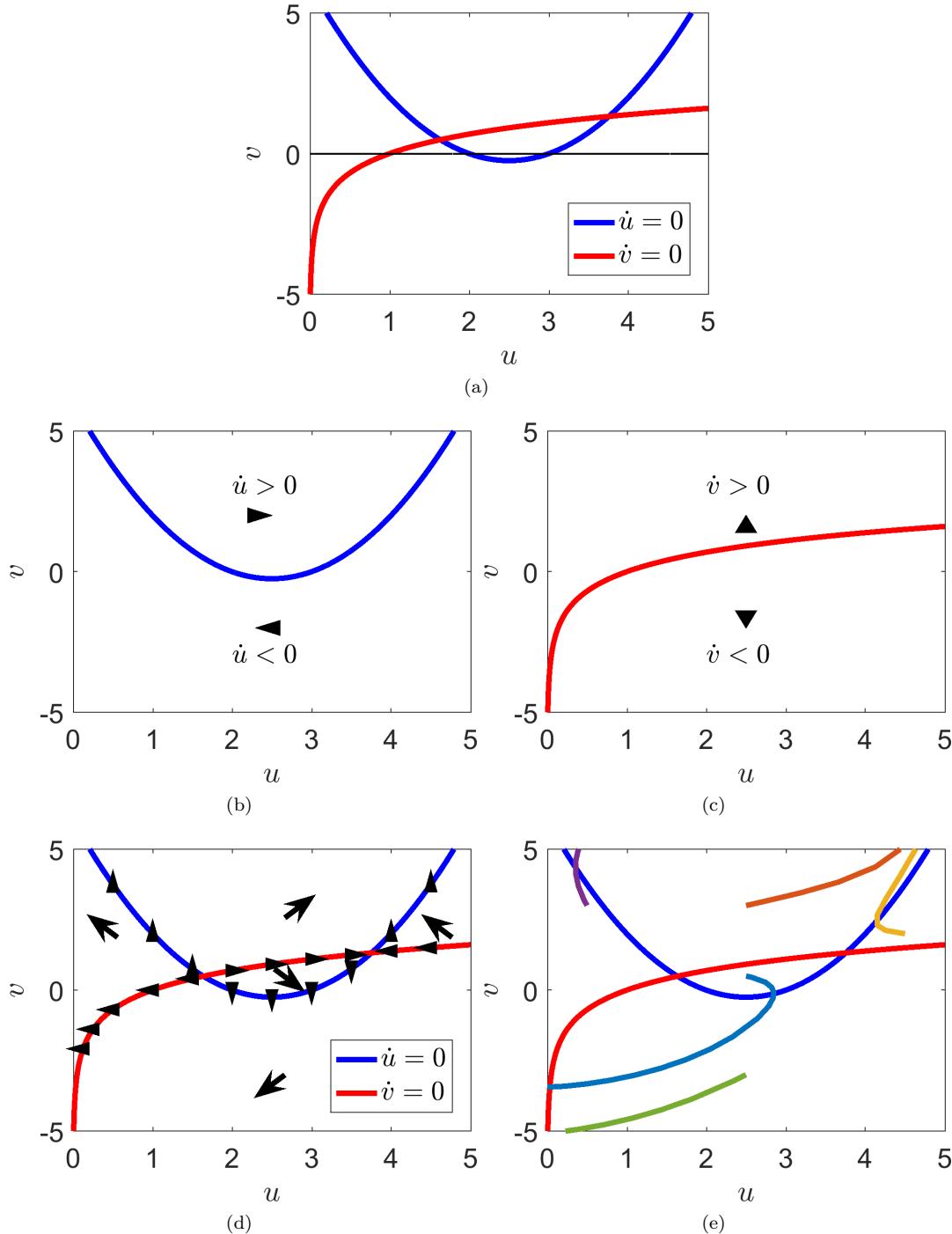


Figure 2.9: (a) Plot of the nullclines of equations (2.41) and (2.42). Specifying the signs of the derivatives on either side of the (b) \dot{u} and (c) \dot{v} nullcline. The arrowheads indicate the general direction that a trajectory will be heading. These results can then be combined into the direction plots seen in (d). Finally, in (e), we simulate a number of trajectories, which demonstrate that the arrows in (d) provide the correct general idea.

- non-dimensionalise a system of equations using direct substitution, or the arrow method;
- sketch simple curves
- derive the steady states and their dependence on any given parameters;
- derive the stability of the steady states and their dependence on any given parameters;
- identify parameter dependent bifurcations;
- define what a nullcline is;
- understand the relationship between steady states and the points at which nullclines cross;
- plot nullclines;
- sketch arrows showing general trajectory directions on the phase plane;
- interpret the stability of the steady states from the information plotted on a phase plane.

Chapter 3

Population modelling

When modelling the changes to any population we must ensure that we include any pertinent production sources and removal sinks. This ensures that we maintain “population conservation”. Namely, all creation and degradation is accounted for in the following word equation (see Figure 3.1),

$$\text{Rate of population change} = \text{Birth Rate} - \text{Death Rate} + \text{Rate of Immigration} - \text{Rate of Emigration}$$

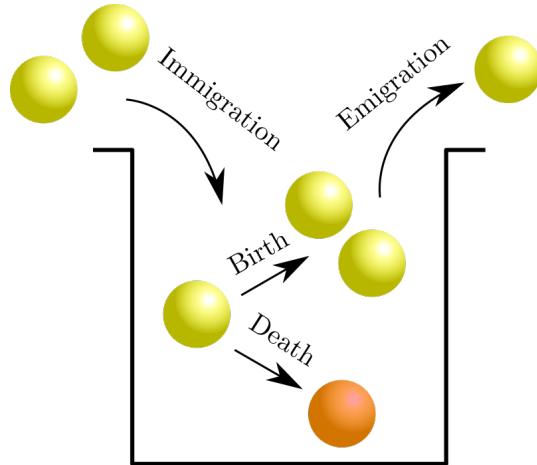


Figure 3.1: Population changes stem from four basic dynamics.

In this chapter we assume that the system is closed and thus there is no emigration or immigration. Namely, we assume that the problem has no spatial variation, or that it is not important. Thus we simply consider the temporal evolution of the system.

3.1 Continuum modelling

There are multiple ways of modelling a population. If there are a large number of individuals in the population and we want to consider how the population changes over continuous time we can use ODEs to define the rules governing the evolution and, hence, predict how the population will fair.

Definition 11. Suppose there exists a function g such that $\dot{u} = f(u)$ can be written as

$$\dot{u} = ug(u) \tag{3.1}$$

then g is known as the *intrinsic growth rate*.

Example 3.1.8 Growth law examples

- The Malthus model, 1798

$$\begin{aligned} u &\xrightarrow{b} 2u, \\ u &\xrightarrow{d} \emptyset. \end{aligned}$$

- The Verhulst Model, 1845. Also commonly known as the Logistic Growth Model.

$$\begin{aligned} u &\xrightarrow{r} 2u, \\ 2u &\xrightarrow{r/K} u. \end{aligned}$$

Example 3.1.9 US population

In 1845 Pierre Verhulst used 60 years worth of population data from the US census and was able to predict the population for the next 100 years. See Table 3.1 and Figure 3.2.

- What goes wrong after 1950 in Figure 3.2(a)?
- In Figure 3.2(b) one of the fitted parameters is $K = 309.3$. What does this mean?
- The US population in 2018 was over 327 million. Should we use the logistic equation to model the US population?

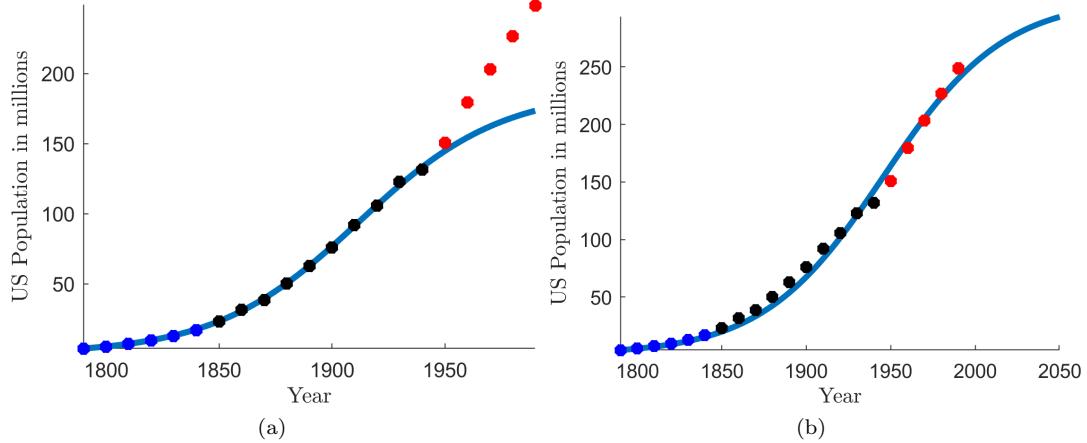


Figure 3.2: (a) The logistic curve fitted by Verhulst in 1845 to US census data. The blue dots are the data known to Verhulst. The black data is the next 100 years worth of data. The initial condition is given by the data $u_0 = 3.929$. The fitted parameters are $K = 188.3$ and $r = 0.0316$. (b) The logistic curve fitted with all data up to 1990. The fitted parameters are $K = 309.3$ and $r = 0.0280$. See example 3.1.9.

Year	US census data in millions	Population prediction in millions
1790	3.929	3.929
1800	5.308	5.346
1810	7.240	7.255
1820	9.638	9.808
1830	12.866	13.195
1840	17.069	17.635
1850	23.192	23.3700
1860	31.443	30.635
1870	38.558	39.616
1880	50.156	50.388
1890	62.948	62.851
1900	75.996	76.681
1910	91.972	91.339
1920	105.711	106.132
1930	122.775	120.346
1940	131.669	133.373
1950	150.697	144.802
1960	179.323	154.455
1970	203.185	162.347
1980	226.546	168.630
1990	248.710	173.527

Table 3.1: US population census data between 1790 and 1990 and the accompanying prediction by the logistic equation. The bold data at the top was all that was known to Verhulst in 1845.



Figure 3.3: Spruce budworm in moth and larval stages.

Example 3.1.10 Spruce budworm

Spruce budworm (see Figure 3.3) are preyed upon by spiders, miscellaneous insects, and birds. A model for their population size, N is given by

$$\dot{N} = RN \left(1 - \frac{N}{K}\right) - \frac{BN^2}{A^2 + N^2}. \quad (3.5)$$

1. What does each term in the equation mean?
2. Describe, with a sketch, three properties of the predation term

$$\frac{BN^2}{A^2 + N^2}. \quad (3.6)$$

Hint: consider low, medium and high values of N .

3. Non-dimensionalise the equation to give the form

$$\frac{du}{d\tau} = \underbrace{ru \left(1 - \frac{u}{k}\right)}_{f_1(u)} - \underbrace{\frac{u^2}{1 + u^2}}_{f_2(u)}. \quad (3.7)$$

4. By sketching the two terms, f_1 and f_2 separately, show there are between 2 and 4 steady states (depending on the values of (r, k)).
5. By considering the $f_1 - f_2$ sketches, characterise the steady state stabilities in all cases.
6. Spruce budworm destroys spruce trees and, so, we would like there population to be extinct. However, what can happen if there is a large outbreak?

1.

2.

3.

$$\dot{N} = RN \left(1 - \frac{N}{K} \right) - BN^2 / (A^2 + N^2), \quad (3.9)$$

4.

•

•

•

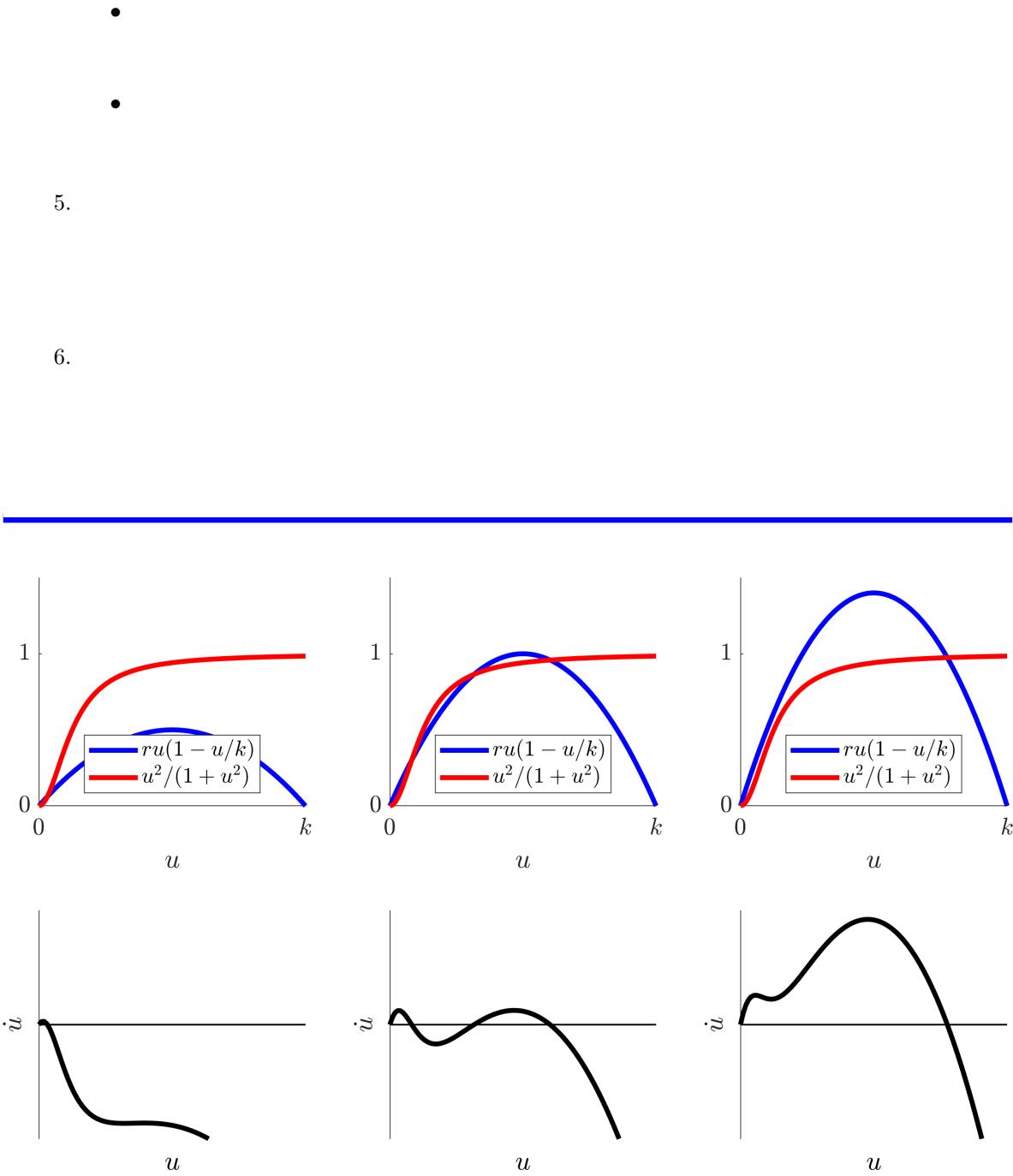


Figure 3.4: Parameter dependence of the Spruce budworm dynamics. r is increasing left to right. The top images are plots of f_1 and f_2 , whilst the bottom illustrates the phase plane $(u, \dot{u} = f_1 - f_2)$.

3.1.1 Disease transmission

The study of infectious diseases has a long history and there are numerous, detailed models of a variety of epidemics and epizootics (i.e. animal epidemics). We can only possibly scratch the surface. In the

following, we consider a simple, framework, model but even this is capable of highlighting general comments about epidemics and, in fact, approximately describe some specific epidemics.

Critically, one of the questions we will seek to answer is when does a disease become an epidemic? Once we have set up the mathematical description of the disease we will see that converting the idea of an epidemic as an increasing number of infections will be fairly simple.

We consider a disease for which the population can be placed into 3 compartments:

- a Susceptible compartment, S , who can catch the disease.
- an Infective compartment, I , who have and transmit the disease.
- a Removed compartment, R , who have been isolated, or who have recovered and are immune to the disease, or have died due to the disease during the course of the epidemic.

In order to derive the equations we make the following assumptions:

- The disease is of short duration course so that the population is constant (counting those who have died due to the disease during the course of the epidemic).
- The disease has a negligible incubation period.
- If a person contracts the disease and recovers, they are immune (and hence remain in the removed compartment).
- The numbers involved are sufficiently large to justify a continuum approximation.

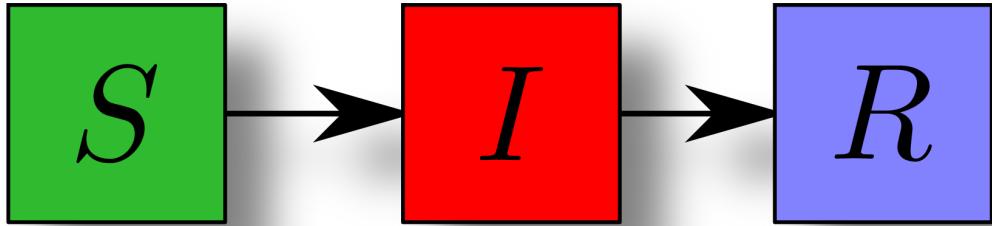


Figure 3.5: Schematic view of a disease transmission. Susceptibles become infectious and, eventually, become removed from the system.

The ‘dynamics’ of the disease can be described by applying a Law of Mass Action to



which provide the following ODEs:

Definition 12. A disease is classed as an epidemic if the number of infections is growing in the population. Explicitly, an epidemic is occurring if $\dot{I} > 0$.

Example 3.1.11 SIR questions

Suppose we know the parameters r and a , which can be estimated from data then we develop methods to approach the following key questions.

1. Noting that R decouples, construct a (S, I) phase plane with nullclines and dynamic arrows to better understand the possible dynamics.
2. Will the disease spread, *i.e.* will the number of infectives increase, at least in the short-term?

Definition 13.

$$\rho = \frac{S_0 r}{a} \quad (3.19)$$

is called the reproduction number. We can interpret ρ as the average number of secondary infections that would be produced by one infective in a wholly susceptible population of size S_0 .

Critically, we see here that an outbreak happens when $\rho > 1$, whilst the infection dies out when $\rho < 1$.

3. What will be the maximum number of infectives at any given time?
 - (a)
 - (b)
 - (c)
 - (d)

$$\implies I(t) - I_0 = -S(t) + S_0 + \frac{a}{r} \ln \left(\frac{S(t)}{S_0} \right). \quad (3.22)$$

]

(e)

4. How many people in total catch the disease?

(a)

(b)

(c)

(d)

(e)

(f)

(g)

(h)

Figure 3.8 shows the SIR model fitted to the COVID-19 pandemic from 2020, for cases in the UK. Although there were many papers published in the months after the virus started to spread they all, pretty much, showed the same thing. This is why the SIR model is so powerful. It is simple, predictive and accurate. However, in the early stages on infection the fitting will be very sensitive.

Note that we do not get the data in the exact (S, I, R) form of the equations. Rather, the daily statistics provided the number of new cases each day, this is the top bar chart. The cumulative sum of this data (which is approximately the integral) should be $C = I + R$, this is the circle data in the bottom graph. We fit to this data (solid line in the bottom graph) to extract out the following predictions $r = 3.34 \times 10^{-6}/(\text{person} \times \text{day})$, $a = 0.537/\text{day}$, $I_0 = 22$ people, $\rho = 1.36$ and $R_\infty = 105,308$ people, where the total population of the UK is $N = 218,829$ people. We then use these fitted parameter values to estimate the data in the top graph (solid line) using dC/dt , since the new cases data should approximate the derivative of C over time. We could fit the new cases data directly. However, as seen in Figure 3.8, this data is noisier than its cumulative summation, thus, fitting to $I + R$ should be more robust to noise and provide a more accurate fitting.

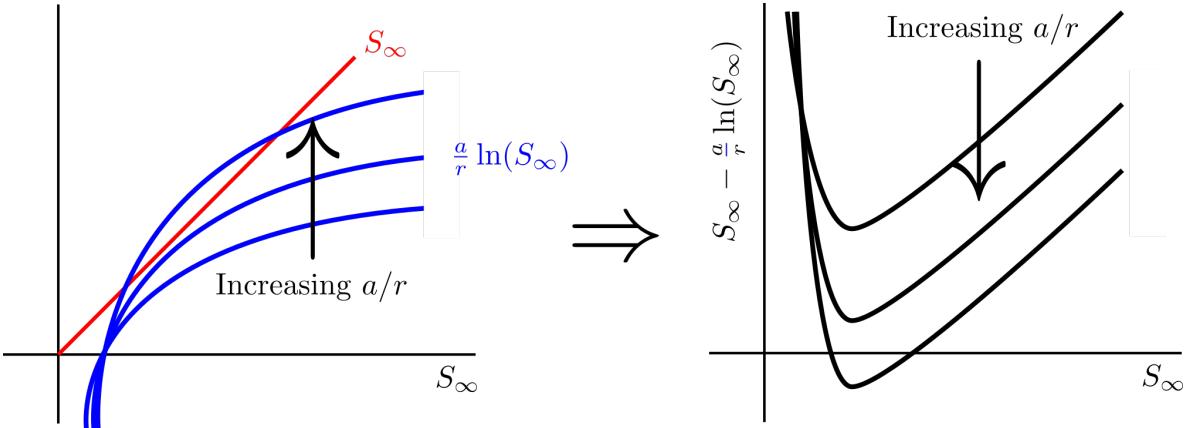


Figure 3.6: Sketching the lines S_∞ and $a \ln(S_\infty)/r$ allows us to sketch $S_\infty - a \ln(S_\infty)/r$.

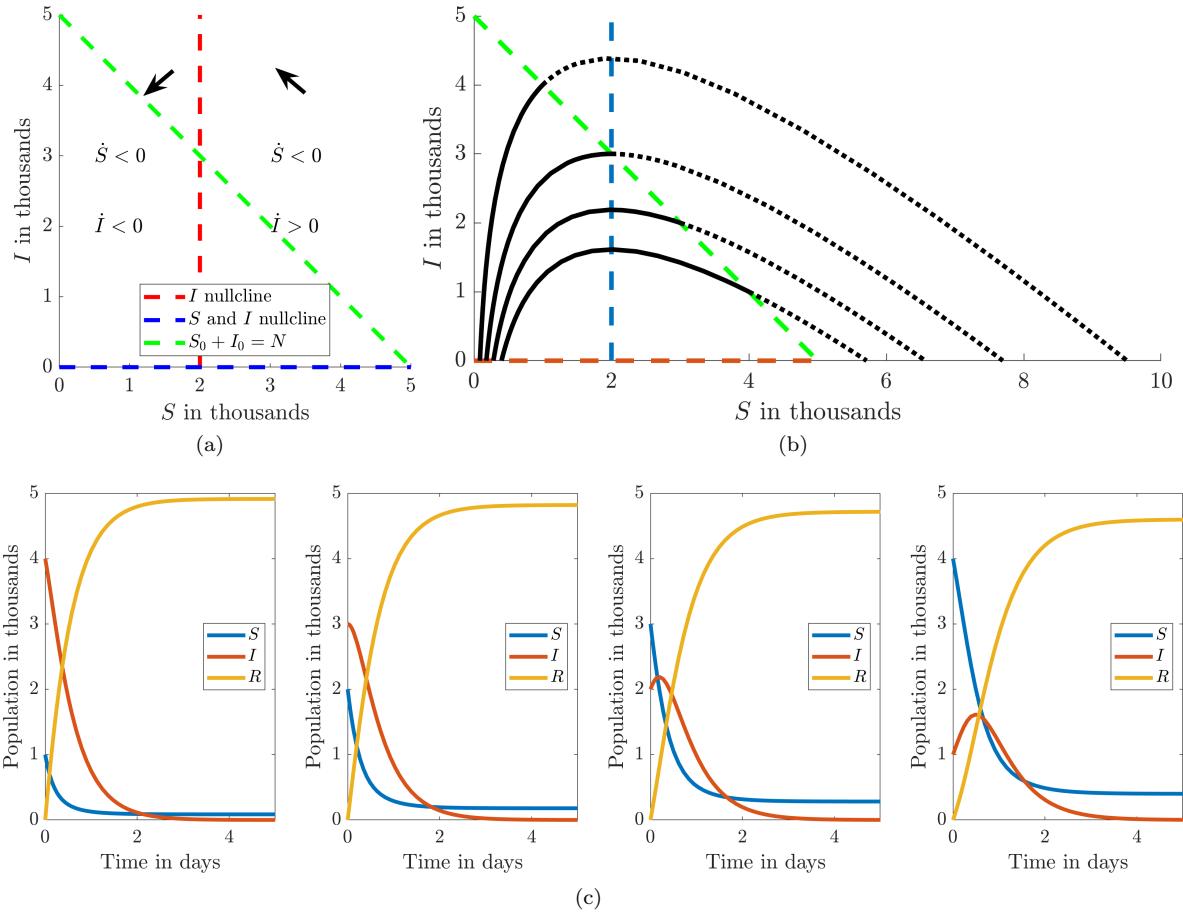


Figure 3.7: Various methods for viewing the dynamics of the SIR system, equations (3.15)-(3.17) with $r = 1/1000/(\text{person} \times \text{day})$ and $a = 2/\text{day}$. The (S, I) phase plane schematic is shown in (a) and is illustrated with trajectories in (b). All initial conditions are on the green dashed line and, thus, the solid lines in (b) are the forward time trajectories, whilst the dashed lines are the backward time trajectories. The four figures in (c) illustrate the (S, I, R) populations of each trajectory in the (b) phase plane. The susceptible (infected) initial condition increases (decreases) left to right.

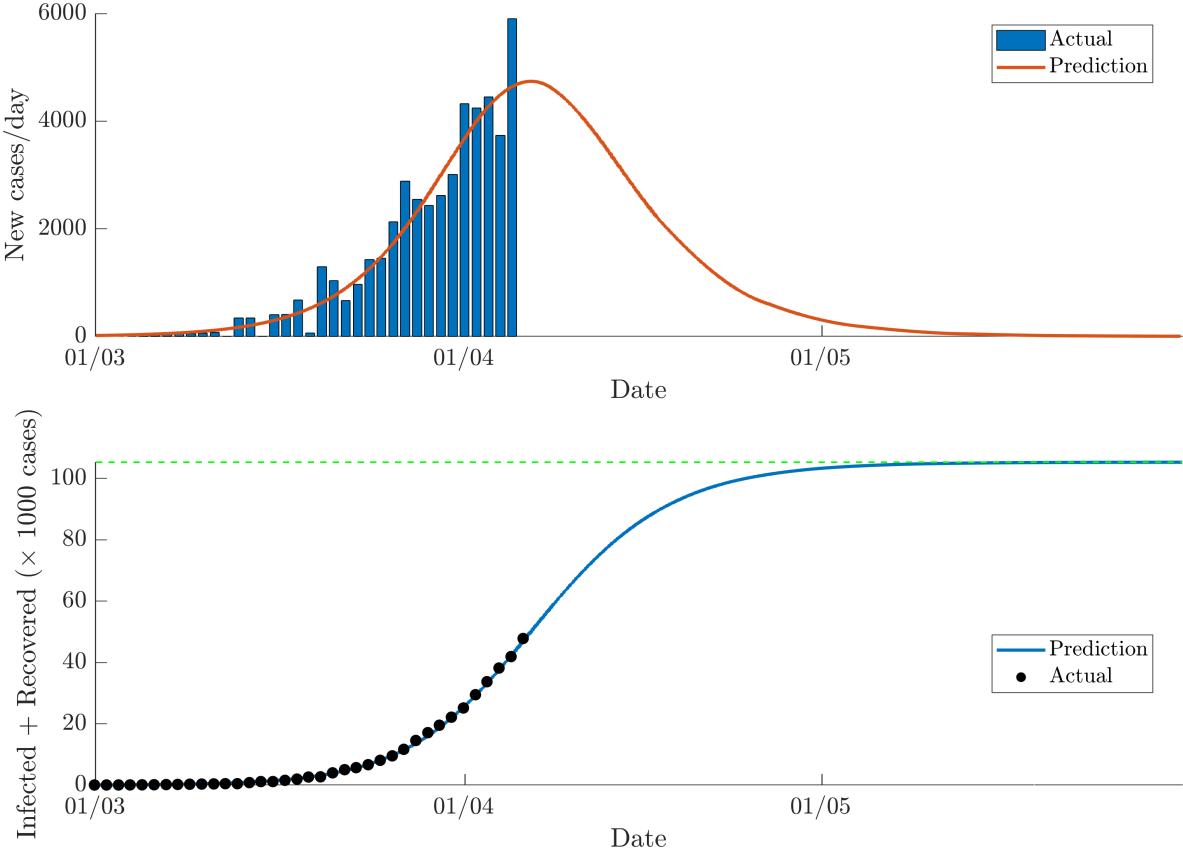


Figure 3.8: Fitting the SIR model to the UK data of new cases from the 2020 COVID-19 pandemic between the 22nd January and 5th April. The top image shows the raw data as a bar chart. The bottom fits $I + R$ (the line) to the cumulative sum of the top data (circles). This provides estimates for the SIR parameters, which are then used to fit the prediction to the top image.

3.2 Discrete modelling

ODEs are one method by which we can model populations. Critically, one of the main assumptions is that the population is dynamically changing in continuous time. This implies that there is a continuous overlap of generations. However, many species have little to no overlap between successive generations and so population growth is in discrete steps.

For example a species of cicada known as the *Magicicada neotredecim* spends almost the full length of its life underground. In the spring of their 13th year the cicadas all appear synchronously and in tremendous numbers. The cicadas develop, mate and die, such that within two months of the original emergence, their life-cycle is complete and the juvenile insects stay underground for another 13 years.

In this case, it would be pointless tracking the population in continuous time. Instead, all we would want to know is how the population at the current time depends on the population 13 years ago. Namely, we would want to construct a function f , such that

$$N_t = f(N_{t-13}). \quad (3.40)$$

In the models we discuss in this chapter we have scaled the time-step to be 1. Models must thus relate the population at time $t + 1$, denoted by N_{t+1} , in terms of the population N_t at time t . This leads us to study difference equations, or discrete models, of the form

$$N_{t+1} = f(N_t), \quad (3.41)$$

where $f(N_t)$ is, in general, a nonlinear function of N_t . Such equations are usually impossible to solve analytically but again we can extract a considerable amount of information about the population dynamics without an analytical solution.

Example 3.2.12 A simple discrete population evolution

Consider

$$N_{t+1} = rN_t, \quad N_0 = n_0. \quad (3.42)$$

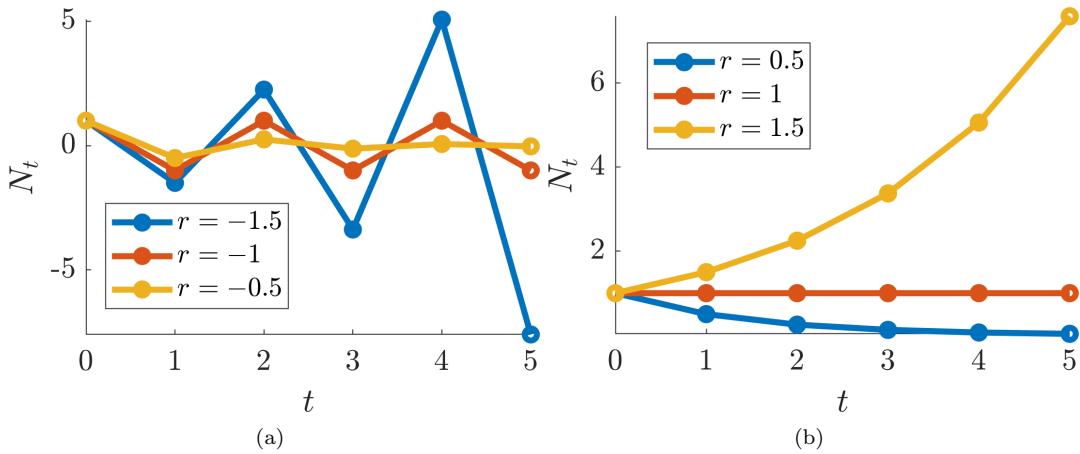


Figure 3.9: Plotting the solution of equation (3.42) with varying values of r . The negative values of r are shown in (a), whilst the positive values are shown in (b).

Definition 14. An steady state N^* of a discrete population model satisfies

$$N^* = f(N^*). \quad (3.45)$$

Such points are also called fixed points, stationary points, or equilibrium points. There are analogous to ODE steady states.

As you might expect, if we have a steady state then we also would like to know if it is stable or not. Namely, similar to ODEs, does a small perturbation away from N^* decay to zero, or does it grow?

Before we answer this question we gain more insight into these equations through plotting their dynamics using a process called cobwebbing.

3.2.1 Cobwebbing

The dynamic evolution of N_t of the general difference equation (3.41) can be obtained graphically through the following algorithm.

1. Create a set of Cartesian axes with N_t along the x -axis and N_{t+1} along the y -axis.
2. Draw the diagonal line $N_t = N_{t+1}$ and sketch the function f , where $N_{t+1} = f(N_t)$.
3. Mark N_0 on the N_t axis. The point N_1 is then given by moving vertically until we intersect the f curve. Specifically, this is the point $N_1 = f(N_0)$.
4. From the point $f(N_0)$ we move horizontally until we intersect the line $N_{t+1} = N_t$, which projects us onto the N_t -axis at N_1 .
5. The process is repeated from line 3 until we can predict the future dynamics of the cobweb map.

Critically, not only will this method provide a quick method of plotting the dynamics of population equation it also provides a means of visualising the steady states. Explicitly, the steady states are where the $N_{t+1} = f(N_t)$ curve intersects the line $N_{t+1} = N_t$.

Example 3.2.13 Cobwebbing the discrete logistic equation

For a generalisation of logistic growth, consider

$$N_{t+1} = rN_t(1 - N_t), \quad N_0 = n_0. \quad (3.46)$$

where $0 < n_0 < 1$. Apply the cobwebbing method to equation (3.46) for different values of r . What happens?

3.2.2 Stability of discrete equations

Similar to continuous systems, finding steady states is only one half of the story. We would like to know whether a steady state is stable or not.

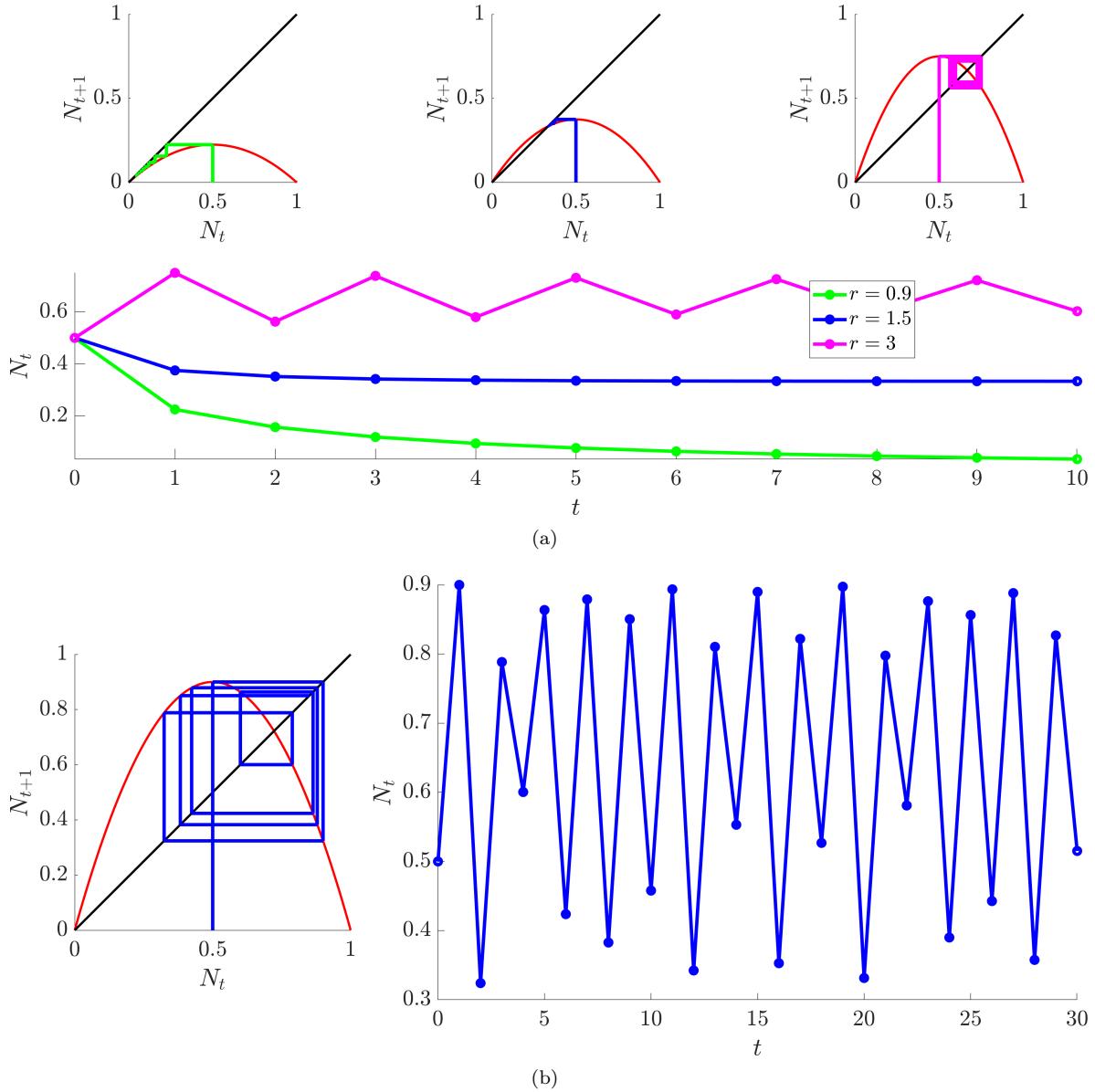


Figure 3.10: Multiple cases of the discrete logistic equation for different values of r . (a) Top row, cobweb diagrams with $r = 0.9, 1.5$ and 3 , left to right, respectively. The accompanying trajectories are plotted in the the bottom image. (b) An example of chaotic dynamics when $r = 3.6$. Left, cobweb diagram. Right, trajectory..

Definition 15. A steady state, N^* , of $N_{t+1} = f(N_t)$ is stable if $\forall \epsilon > 0 \exists \delta, T > 0$ such that whenever $|N_t - N^*| < \delta$ then $|N_t - N^*| < \epsilon \forall t > T$. Otherwise the state is unstable.

Similar to the continuous system, the proof behind the criterion for stability depends upon linearising the system. Namely, we expand the system near a steady state and ask whether a small perturbation will grow, or decay.

Theorem 3.2.1. Suppose N^* is a steady state of the discrete equation

$$N_{t+1} = f(N_t) \quad (3.47)$$

and assume that $f'(N^*) \neq 0$. N^* is stable if $|f'(N^*)| < 1$ and unstable if $|f'(N^*)| > 1$. Further, near N^* , in either case of stability, the trajectories are monotonic if $f'(N^*) > 0$ and oscillatory if $f'(N^*) < 0$.

Proof.

□

Example 3.2.14 Discrete logistic equation revisited

As noted in example 3.2.13 the steady states of the discrete logistic equation are $N^* = 0$ and $1 - 1/r$. Suppose we only consider the case when $r > 0$. Characterise the linear stability of the two steady states.

seen in Figure 3.11.]

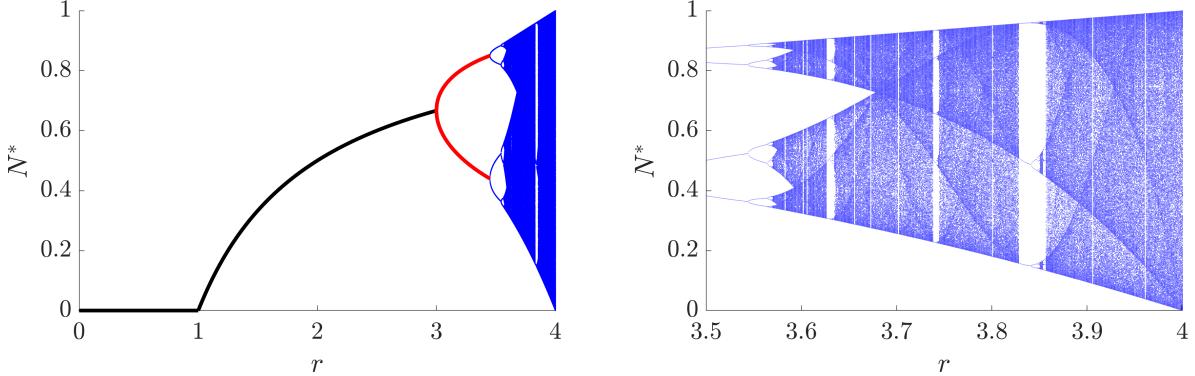


Figure 3.11: Bifurcation diagram of the discrete logistic equation (3.46). On the left we see the derived regions of stability for $N^* = 0$ and $1 - 1/r$ (black line) from example 3.2.14. In example 3.2.15 we will also derive the values and region of stability of the period 2 oscillatory states (red line). However, the derivation of the activity in the blue region is outside the scope of the course, although we can simulate it easily. The right image shows a magnification of the region $3.5 < r < 4$, which illustrates that the discrete logistic system can produce a chaotic trajectory.

3.2.3 Oscillatory states in discrete equations

Definition 16. We define the p^{th} iterate of a map to be the p th time step. Namely

$$f^p(N_t) = \underbrace{f(f(\dots f(N_t) \dots))}_{p \text{ times}} = N_{t+p}. \quad (3.52)$$

Definition 17. A state, N^* , has an oscillatory period p if p is the smallest integer such that $N^* = f^p(N^*)$.

Theorem 3.2.2. Suppose $N_{t+1} = f(N_t)$ has an oscillatory point, N^{1*} , of period p . Then there are also $p - 1$ distinct points that have oscillatory period p .

Proof.

□

Definition 18. The orbit of an oscillatory point, N^{1*} with period p , of a map f , is the set of points $\{N^{1*}, N^{2*} = f(N^{1*}), N^{3*} = f(N^{2*}) = f^2(N^{1*}), \dots, N^{p*} = f(N^{(p-1)*}) = f^{(p-1)}(N^{1*})\}$.

As seen in figures 3.10(a) and 3.11, when r increases past 3 there is no longer a single steady state. Rather the system undergoes a bifurcation to an oscillatory trajectory of period 2. Further, Figure 3.11 shows that around $r \approx 3.5$ the system bifurcates again into a period 4 oscillation. As r increases further a cascade of bifurcations happen leading to states with higher periods of oscillations, demonstrating that that the discrete logistic system can produce chaotic trajectories.

As you might expect, understanding the full chaotic region is extremely complicated. However, we can move beyond just the steady states to consider the simple oscillatory states. For example, suppose a system has a period 2 oscillation, *i.e.* there are two (non-equal) states, N_1^* and N_2^* , such that $N_1^* = f(N_2^*)$ and $N_2^* = f(N_1^*)$. Each state is then a steady state of f^2 , *i.e.*

$$f^2(N_1^*) = f(f(N_1^*)) = f(N_2^*) = N_1^*. \quad (3.57)$$

Theorem 3.2.3. If N^* is an oscillatory state of f , of period p , it is a steady state of f^p .

Proof. Practically by definition. □

Theorem 3.2.4. Suppose N^* is an oscillatory state of period m , where m is a factor of p then N^* is also a steady state of f^p .

Proof.

□

From theorems 3.2.3 and 3.2.4 we have a way of finding periodic states. From stability theorem 3.2.1 we also have a way of characterising the stability of a period p oscillation, namely, x_p is a stable period p oscillation of the map f if x_p is a stable state of the map f^p . Explicitly,

$$x_p \text{ is } \begin{cases} \text{stable if } \left| \frac{df^p(x_p)}{dx} \right| < 1, \\ \text{unstable if } \left| \frac{df^p(x_p)}{dx} \right| > 1. \end{cases} \quad (3.58)$$

However, calculating $df^p(x_p)/dx$ often requires difficult algebraic manipulations. Thankfully, the following theorem simplifies the issue.

Theorem 3.2.5. Let x^{1*} be a period p oscillation of f then

$$\frac{df^p(x^{1*})}{dx} = f'(x^{1*})f'(x^{2*})f'(x^{3*}) \dots f'(x^{p*}), \quad (3.59)$$

where $x^{i*} = f^{i-1}(x^{1*})$.

Proof.

□

Thus, instead of evaluating the derivative of the p th iteration map we need only calculate the derivative of the original map and evaluate it at all period p steady states. This evaluation may not be easier, but it should be easier than evaluating the derivative of the p th iteration map. This also then leads to the following observation

Corollary 3.2.6. *The stability of all periodic points in the same orbit is the same, namely,*

$$\frac{df^p(x^{1*})}{dx} = \frac{df^p(x^{2*})}{dx} = \dots = \frac{df^p(x^{p*})}{dx}. \quad (3.62)$$

Proof.

□

Example 3.2.15 Period 2 oscillations in the discrete logistic equation

Derive the period two oscillation states specifying their existence and stability dependence on r .

]

]

3.3 Check list

By the end of this chapter you should be able to:

- reproduce all definitions;
- state and prove all theorems, where proofs are given;
- construct ODE models from descriptions;
- manipulate and investigate ODE models using combinations of methods from Chapter 2 to solve specific questions;
- generalise presented results to variations of the SIR model;
- derive steady states and oscillatory states from discrete time population equations;
- use cobwebbing to suggest the stability of steady states from discrete time population equations;
- characterise the stability of steady states and oscillatory states from time discrete population equations;

Chapter 4

Spatial systems

So far we have considered biological phenomena with negligible spatial variation. Many times, however, space is very important. For example, in ecological contexts you do not normally find predator and prey living together; animals often have to leave their home roosts to find food, wolves, for example.

An alternative example can be seen in the interactions of grey and red squirrels in the UK. Here, one species invades another's territory. Modelling helps us understand how the populations will evolve, *e.g.* will one populations win out, or will the populations eventually separate the land and coexist? Equally, the modelling can inform us of how to reduce the invasive risk of the population.

There are two main forms of motion we are going to consider, random motion and directed motion.

Definition 19. *Diffusion is the random movement of system agents. (see Figure 4.1(a))*

Definition 20. *Taxis is the directed movement of system agents. (see Figure 4.1(c))*

Note there are many forms of taxis, specifying what is causing the directional motion for example:

- **chemotaxis** is when the agents move up (chemoattractant) or down (chemorepellent) a chemical gradient.
- **galvanotaxis** is movement induced by electric fields.
- **gravitaxis** is movement that responds to gravity.

4.1 Deriving the diffusion equation

We will first derive the equation behind diffusion, then taxis. Further, in each case, we consider motion in the infinite domain case and then add boundaries, as these are minor complications that modify the main derivation.

All derivations follow the process of discretising a continuum population. The separation between the discretised points is then taken to zero in an appropriate limit leading to the desired equation.

Theorem 4.1.1. *The model for random motion of a population u on an infinite line is*

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2}, \quad (4.1)$$

where D is defined to be the diffusion coefficient, a positive constant that specifies the rate at which the population spreads out.

Note that since there are no boundaries we do not need to consider boundary conditions. However, an initial condition needs to be supplemented to close the model, fully. See Figure 4.4(a) for an illustrated example.

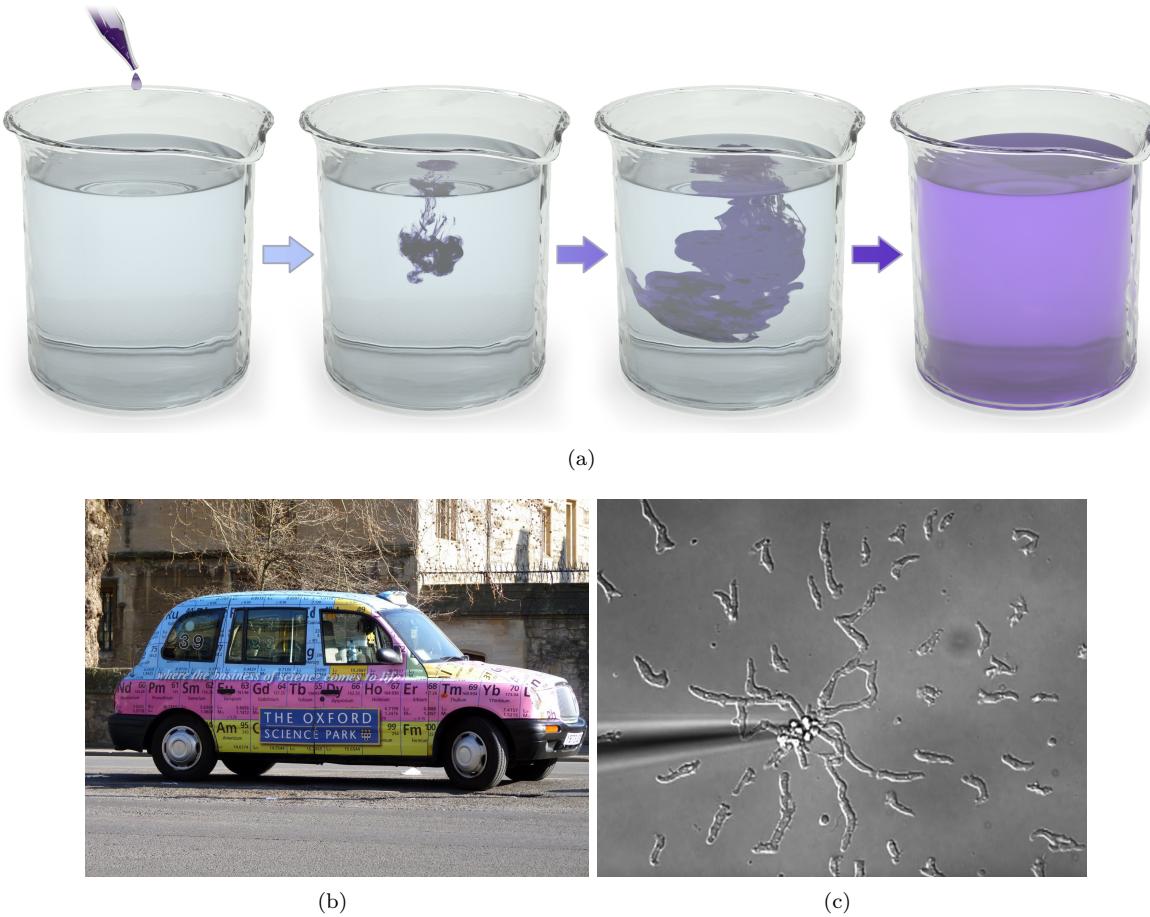


Figure 4.1: Illustrating (a) diffusion, (b) chemotaxis and (c) actual chemotaxis. In (a), as long as the water is not stirred, or heated, the ink will undergo diffusion. The ink has no directed motion, the water and ink particles bump together causing the ink to spread out to a homogeneous state. In (c) slime mould cell (*Dictyostelium*) is attracted to a pipette full of cyclic adenosine monophosphate (cAMP).

Proof.

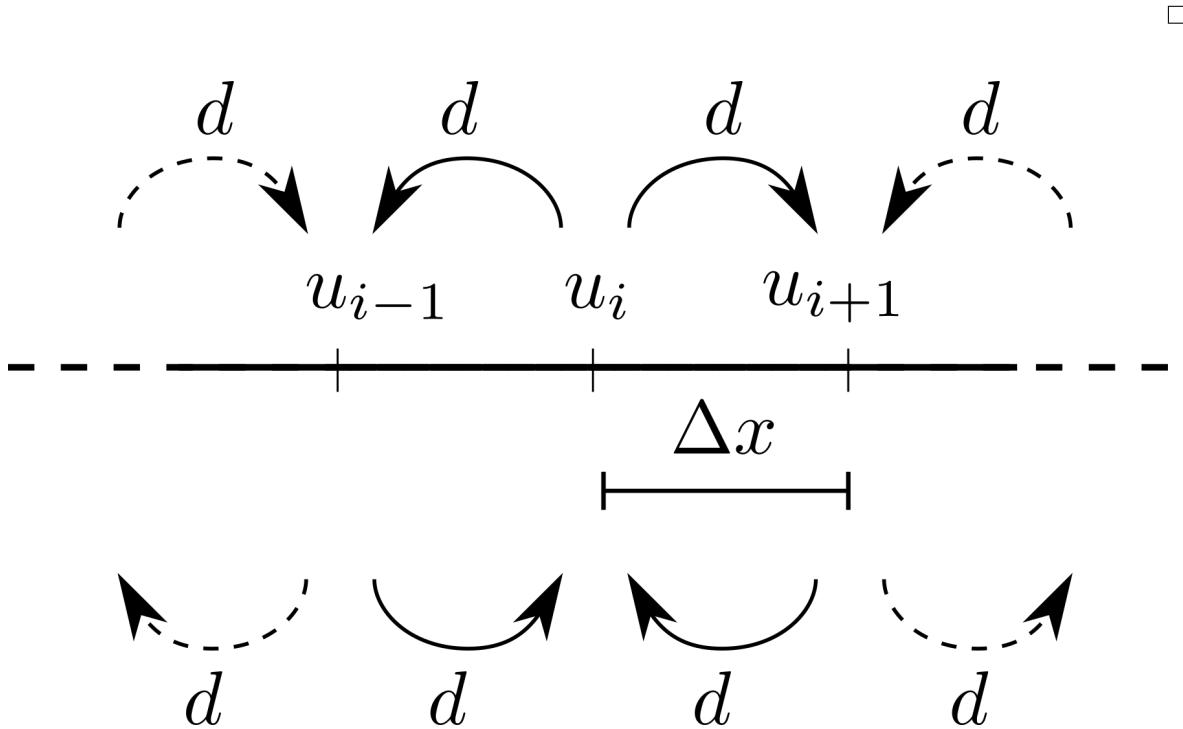


Figure 4.2: Diffusion schematic.

We now consider boundary conditions. Specifically, there are three main types: Dirichlet, Neumann and Robin (all named after dead mathematicians).

Definition 21. *Dirichlet boundary conditions fix the value of the variable on the boundary to be a constant.*

For example, $u(0, t) = \alpha$ and $u(L, t) = \beta$, for $\alpha, \beta \geq 0$ are perfectly valid Dirichlet boundary conditions for the one-dimensional diffusion equation. See Figure 4.4(c) for an illustrated example.

Definition 22. *Neumann boundary conditions fix the value of the variable's derivative on the boundary to be a constant.*

For example,

$$\frac{\partial u(0, t)}{\partial x} = \alpha \quad \text{and} \quad \frac{\partial u(L, t)}{\partial x} = \beta \quad (4.8)$$

are perfectly valid Neumann boundary conditions for the one-dimensional diffusion equation.

Definition 23. *Robin boundary conditions fix a linear combination of the variable's value and derivative on the boundary to be a constant.*

For example,

$$\alpha_1 u(0, t) + \alpha_2 \frac{\partial u(0, t)}{\partial x} = \alpha_3 \quad \text{and} \quad \beta_1 u(L, t) + \beta_2 \frac{\partial u(L, t)}{\partial x} = \beta_3 \quad (4.9)$$

are perfectly valid Robin boundary conditions for the one-dimensional diffusion equation.

Although there are infinitely more we will generally only consider the first two. Equally, a system is able to have different boundary conditions on each boundary.

Critically, the Neumann boundary conditions model the flux in, and out, of the domain. We will now show that when we consider an insulated domain (in which no substance enters or leaves through the boundary) then we are considering the specific case of Neumann boundary conditions in which $\alpha = \beta = 0$ in equation (4.8). These are specifically called zero-flux, or reflective boundary conditions.

Theorem 4.1.2. *Consider a diffusing population in a finite one-dimensional domain, $[0, L]$. Further, suppose this substance is unable to leave the domain when zero-flux boundary conditions are applied. We will show that the mathematical model of this situation is*

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2}, \quad (4.10)$$

supplemented with the boundary conditions

$$\frac{\partial u(0, t)}{\partial x} = \frac{\partial u(L, t)}{\partial x} = 0. \quad (4.11)$$

As above, an initial condition needs to be supplemented to close the model, fully. See Figure 4.4(b) for an illustrated example.

Proof.

□

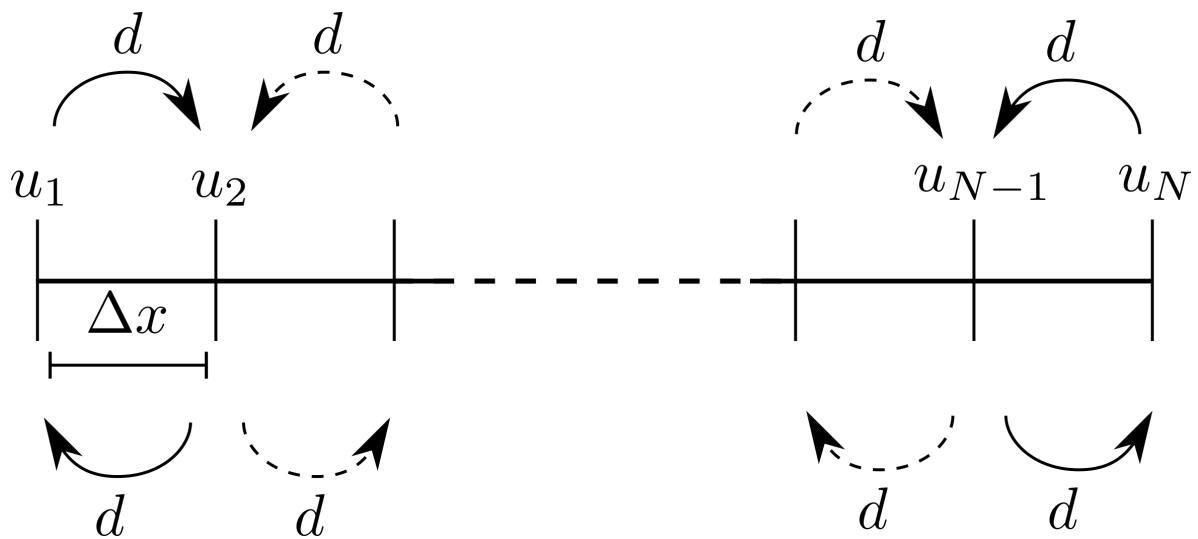


Figure 4.3: Diffusion schematic within an insulated domain.

Theorem 4.1.3. Consider a one-dimensional diffusing population. In the case of a zero-flux boundary conditions, the population total does not change.

Proof.

□

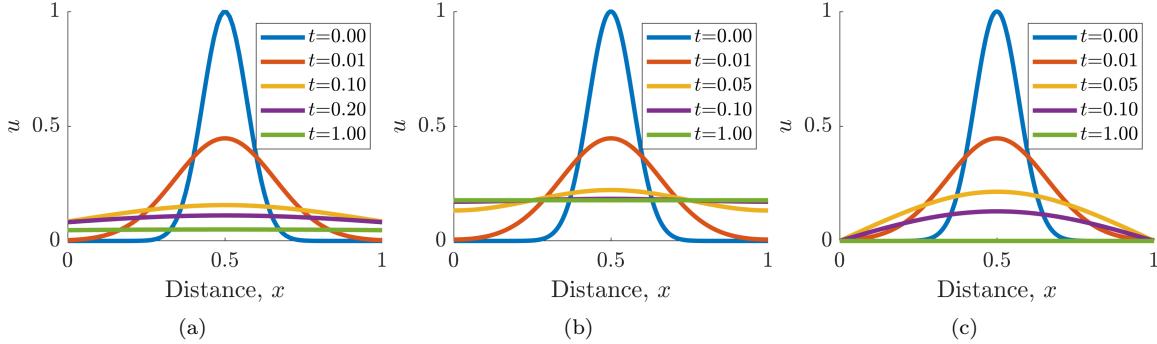


Figure 4.4: Illustrating diffusion on (a) an infinite domain, (b) a finite domain with zero-flux boundaries and (c) a finite domain with zero-Dirichlet boundaries. Parameter value $D = 1$ in all cases. The initial condition in all cases was $u(x, 0) = \exp(-((x - 1/2)10)^2)$.

4.2 Deriving the taxis equation

In the last section we saw that the diffusion equation required the second spatial derivative. The derivation of the taxis equations follow exactly the same argument, but we will see that the taxis equation only requires the first spatial derivative. This is simpler to derive, but we started with the more complicated equation because we will be using diffusion more often and it was important to get ourselves used to the derivation argument.

Theorem 4.2.1. *Consider a one-dimensional domain filled with a population u that is subject to two different spatially dependent forces. One force attracts the population to the left, causing a flux of movement at a rate, $d_l(x) = D_l(x)/\Delta x$, whilst the other attracts the population to the right, causing a flux of movement at a rate $d_r(x) = D_r(x)/\Delta x$. The equation controlling the populations evolution is then*

$$\frac{\partial u}{\partial t} = \frac{\partial ([D_l(x) - D_r(x)]u)}{\partial x}. \quad (4.17)$$

Since we are on an infinite domain we simply have to assume that the solution stays finite and initial conditions are required to close the solution.

Proof.

□

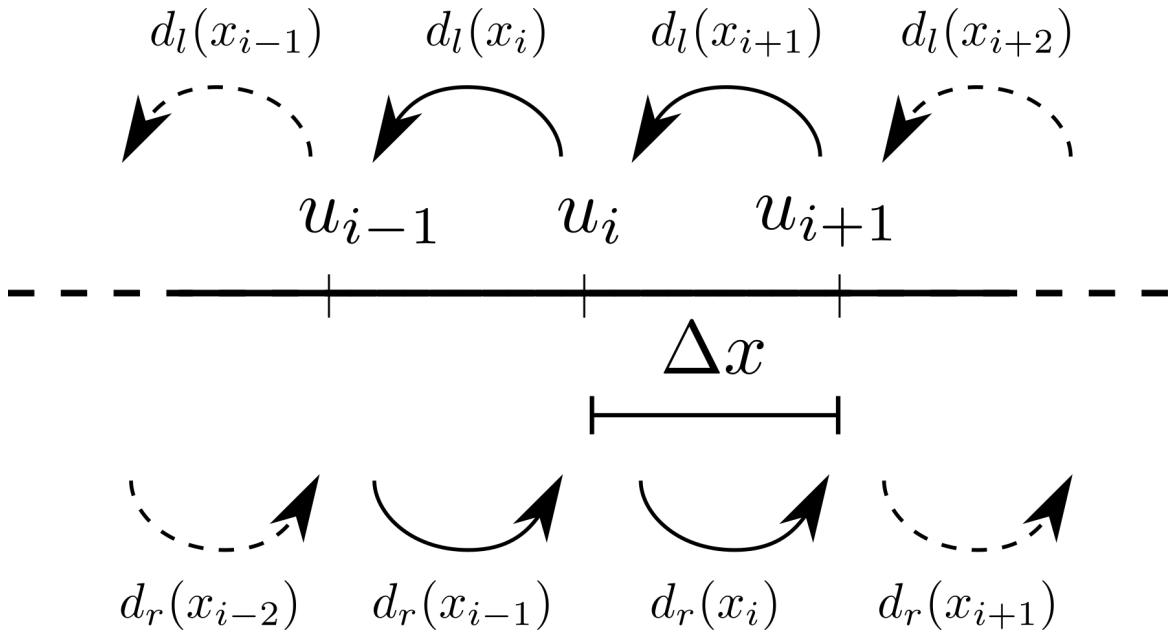


Figure 4.5: Taxis schematic.

4.3 Travelling waves

In previous chapters we have developed a theoretical framework of interacting species. Such interactions can simply be added to models of spatial motion. Namely, if $f(u, v)$ and $g(u, v)$ are interaction kinetics for populations u and v then

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u, v), \quad (4.24)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + g(u, v), \quad (4.25)$$

would be a one-dimensional spatial extension of the reaction kinetics, assuming that populations u and v diffused with rates D_u and D_v , respectively.

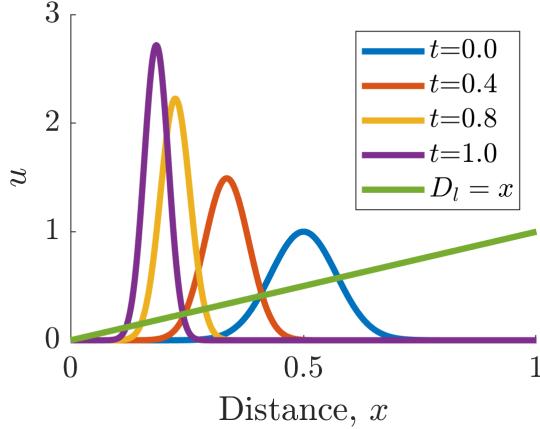


Figure 4.6: Illustrating taxis on a finite domain with zero-flux boundary conditions with $D_l = x$ and initial condition $u(x, 0) = \exp(-((x - 0.5)10)^2)$.

However, before we consider the possibilities of two interacting populations, we consider the simple example of combining logistic growth and diffusion in one spatial dimension. Critically we are going to look conditions under which *Fisher waves* can form

Definition 24. *A Fisher wave is a specific form of travelling wave solution that translates in space at a constant speed over time, without changing its shape.*

4.3.1 Fisher's equation

Example 4.3.16 Fisher waves in Fisher's Equation

Consider the following system

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + ru \left(1 - \frac{u}{K}\right), \quad (4.26)$$

on an infinite domain, subject to the following boundary and initial conditions:

$$u(x, t) \rightarrow u_{\pm\infty} \text{ as } x \rightarrow \pm\infty \text{ and } u(x, 0) = u_0(x). \quad (4.27)$$

where $u_{\pm\infty}$ are constants to be determined and $u_0(x)$ is any function satisfying the boundary conditions. This equation is known as Fisher's equation and it was first proposed to model the spread of an advantageous gene through a population.

We will show that Fisher waves, as defined in definition equation (24), can be supported by equation (4.26). We will be led by our intuition of what we expect the waveform to look like (see Figure 4.7). Namely, from our understanding of the logistic equation any small perturbation to zero leads the population to grow to the carrying capacity. Thus, we expect that large populations will invade small populations until everywhere is at $u = K$.

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Theorem 4.3.1 (The Poincaré-Bendixson Theorem). *For a system of two first order ordinary differential equations, consider a closed bounded region, R . Suppose a trajectory, $\mathbf{p}(t) = (u(t), v(t))$, lies entirely within R . Then one of the following is true:*

- (a) $\mathbf{p}(t)$ is a closed trajectory, e.g. a limit cycle;
- (b) $\mathbf{p}(t)$ asymptotically tends to a closed trajectory, e.g. a limit cycle;
- (c) $\mathbf{p}(t)$ terminates at a stationary point.

Therefore, if R does not have a stationary point then there must be a limit cycle. Equally, if R does not contain a limit cycle then the trajectory must terminate.

Proof. Nonexaminable, but, for the interested, see P. Glendinning, Stability, Instability and Chaos: An Introduction to the Theory of Nonlinear Differential Equations. \square

5.

^aAlthough our mathematics is specifically for an infinite domain, we, of course, cannot simulate this. Thus, often mathematicians simulate “large” domains and consider the solution far away from the boundaries. However, what “large” means is heavily context dependent.

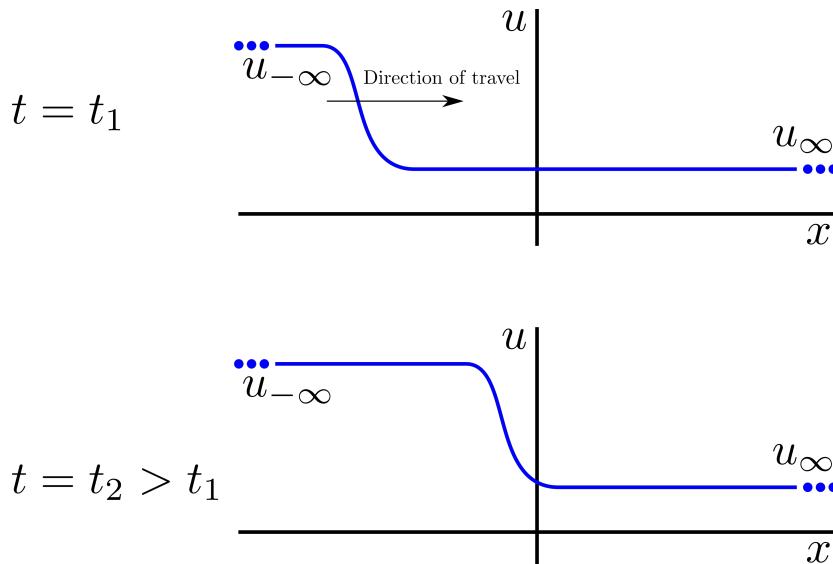


Figure 4.7: Schematic diagram of what a Fisher wave should look like, to aid our intuition.

4.4 Check list

By the end of this chapter you should be able to:

- reproduce all definitions;
- state and prove all theorems, where proofs are given;
- derive the taxis and diffusion PDE forms from discretised domains;
- derive appropriate boundary condition from discretised domains;
- specify what different boundary conditions mean;
- convert PDEs to travelling wave coordinates;
- derive conditions underwhich travelling waves could form.

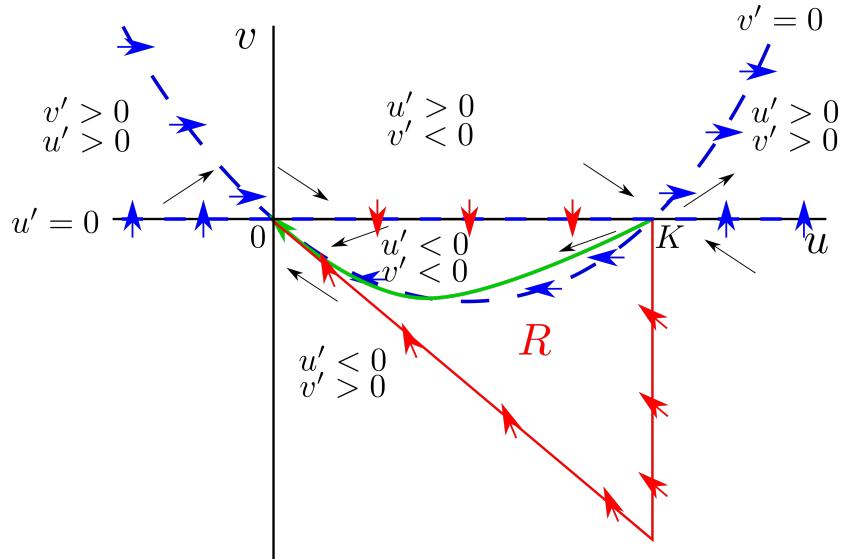


Figure 4.8: Phase plane of the Fisher equation in moving coordinates, equations (4.34) and (4.35).

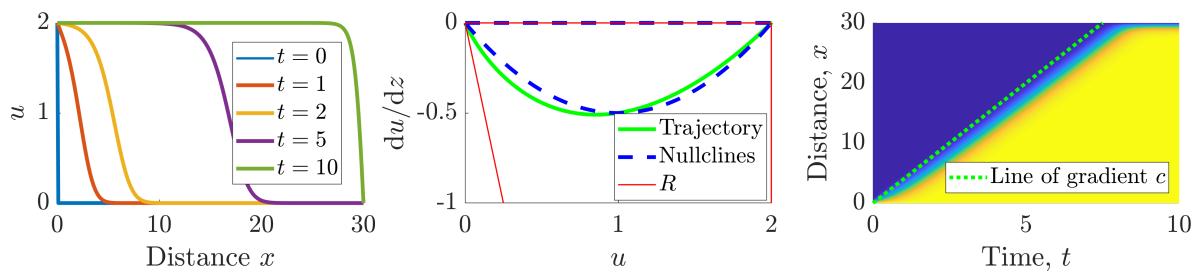


Figure 4.9: Simulation of Fisher's equation (4.26) presented in a number of ways. Left: Different time points of the wave profile. Middle: Phase plane with added simulated trajectory. Right: Time-space plot of u . Parameters $r = 4$, $D = 1$ and $K = 2$.

Chapter 5

Pattern Formation

Examples of the importance of spatial patterning and structure can be seen just about everywhere in the natural world (see Figure 5.1). Here, we will be concerned with building and analysing models which can generate such patterns. Specifically, we want to see how simplicity can lead to complexity.



Figure 5.1: Examples of spatial patterning.

Definition 25. *Patterns are stable, time-independent, spatially heterogeneous density profiles.*

Definition 26. *Morphogens are pattern forming agents. They can be proteins, cells, animals, etc.*

5.1 French flag patterning

One of the most common mechanisms of pattern creation is that of using cells to read local concentrations of morphogens. If all cells sense the same concentration then they will all differentiate to be the same type of cell. However, if there is a heterogeneous spread of morphogen then we can define thresholds, $T_1 > T_2$ such that cells that sense a morphogen level greater than T_1 will differentiate differently to those that sense a morphogen amount lower than T_2 (see Figure 5.2). The question thus becomes, how does one generate a heterogeneous morphogen profile?

One of the simplest methods of producing a heterogeneous morphogen profiles is to have heterogeneous production of morphogen. In this section, we will consider isolated regions of production

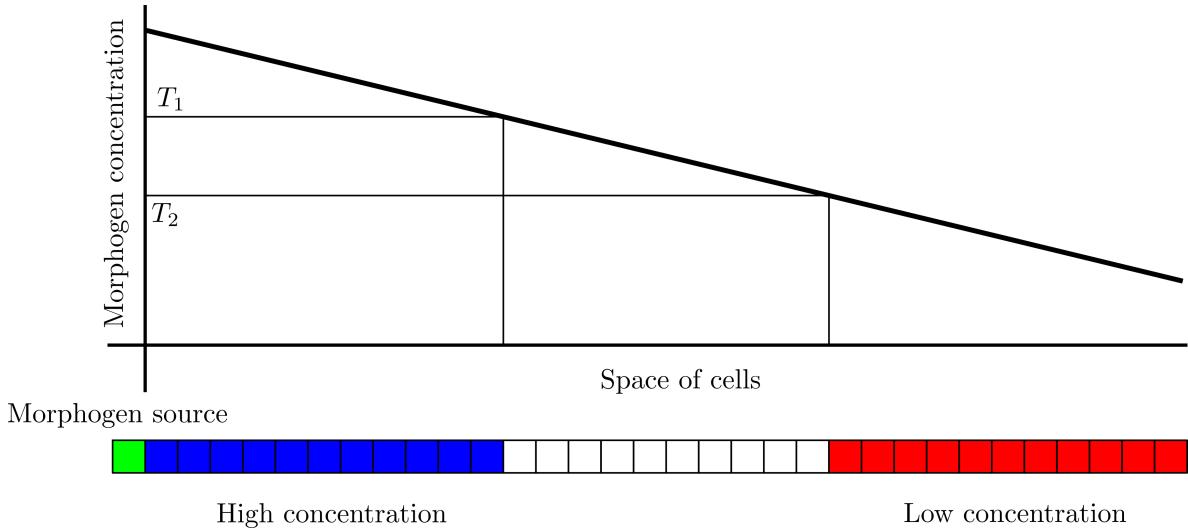


Figure 5.2: Schematic mechanism of French flag patterning.

and consider the morphogen pattern that arise. This is known as French flag patterning (see Figure 5.2).

Example 5.1.17 Localised source

Consider a morphogen u produced at $x = 0$. The morphogen is able to diffuse into the one-dimensional tissue interval $[0, L]$, with diffusion rate D . We assume further that the morphogen cannot leave through the boundary $x = L$, i.e. it is a reflective boundary. Further, assume that as the morphogen travels it decays at a rate proportional to itself. The mathematical model of this situation is

$$\frac{\partial u}{\partial t} = \underbrace{D \frac{\partial^2 u}{\partial x^2}}_{\text{Diffusion}} - \underbrace{\gamma u}_{\text{Decay}}, \quad (5.1)$$

$$\underbrace{u(0, t) = S}_{\text{Dirichlet condition as a boundary source}}, \quad \underbrace{\frac{\partial u}{\partial x}(L, t) = 0}_{\text{Zero-flux condition at the right-hand side}}, \quad (5.2)$$

$$\underbrace{u(x, 0) = 0}_{\text{Initially, there is no morphogen in the field}}. \quad (5.3)$$

Note that initial condition do not satisfy the boundary condition. Thus, we expect there would be a singularity in the solution as $t \rightarrow 0$. Although we are able to solve this equation using a separable solution, i.e. $u(x, t) = f(x)g(t)$, and Fourier series we are more interested in the steady state situation. Namely, what is the shape of u far into the future?.

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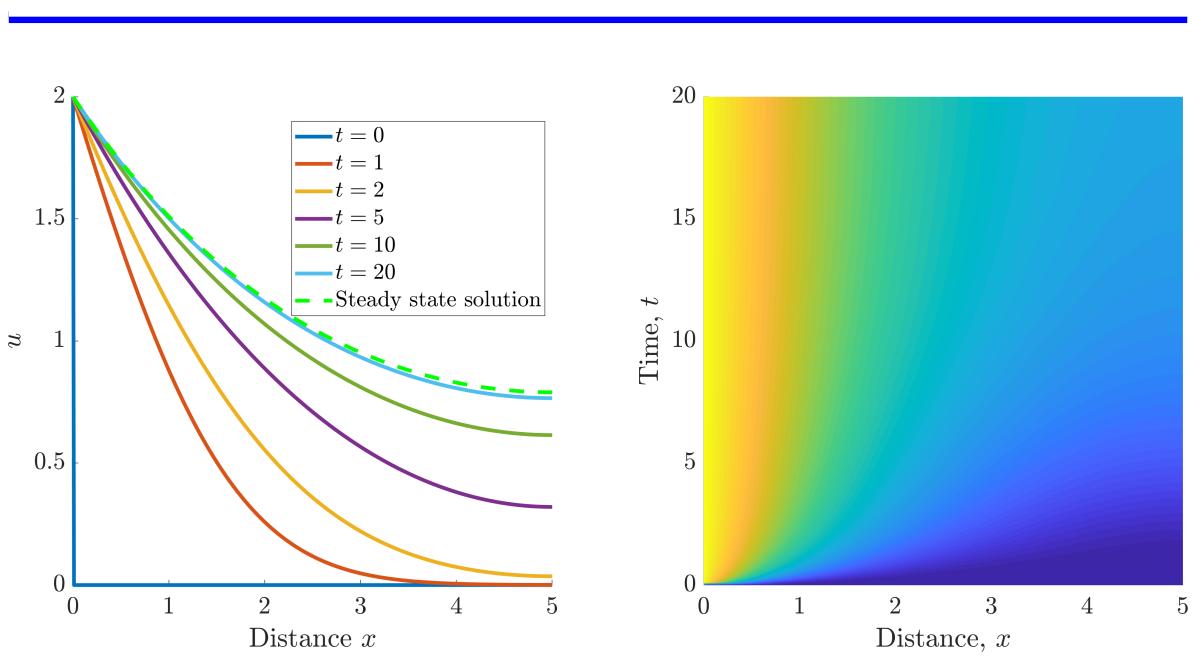


Figure 5.3: Simulation of equations (5.1) and (5.3). Parameters $L = 5, D = 1, \gamma = 0.1$ and $S = 2$.

5.1.1 Digit specification in the limb bud

One successful applications of the French flag model is in understanding chick limb development (see Figure 5.4). Biologists have identified a region, called the “polarising zone”. This small region of cells exists towards the posterior of the chick limb bud and is a localised source of a protein called “Sonic Hedgehog”¹, or Shh for short.

Shh diffuses out from the polarising zone and appears to specify digit formation through a concentration dependent mechanism. Critically, to really cement the idea that the digits are specified through a French flag mechanism biologists perturbed the limb bud system by adding a second polarising region to the anterior part of the limb bud (see Figure 5.4(c)). The experimental system gave rise to chicks with extra digits, but, more importantly, the digit identities were reversed. Such results are predicted exactly by adding a second boundary source to equation (5.1). Further, if the second source has a reduced strength then, as we would expect from a concentration dependent, development the extra development never forms the digits that require the highest levels of Shh.

Of course, this is not the end of the story. More recent work in this area suggests that digit specification is not only dependent on the spatial concentration of Shh that the cells sense, but also the amount of time which they are able to sense the concentration. Thus, a high concentration of Shh causes the first digit to develop. However, if we remove the high concentration too early we are left with a digit that is more akin to the final digit that develops.

What you should take from this is that although we have many tools to understand parts of biological development we still do not fully understand the whole. An idea that nicely transitions us to the next section, where understanding each mechanism separately does not provide an understanding of the whole.

5.2 The Turing instability

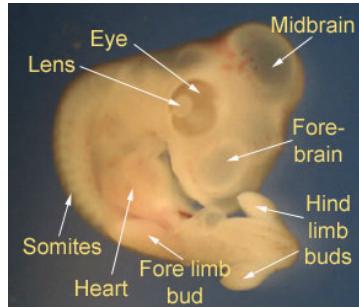
Although the French flag mechanism is able to produce long-range patterns it still requires heterogeneity to be built into the system. We now consider a patterning mechanism that can produce spatial structure from randomness.

In 1952, the logician, computer scientist, code breaker and mathematician Alan Turing proposed a novel mathematical model for pattern formation. He hypothesised that the patterns we see arise due to cells responding to underlying *pre-patterns* of chemical concentrations. He termed these chemicals *morphogens*, and showed that spatially heterogeneous patterns could arise in systems in which these chemicals reacted with each other and also underwent diffusion - a phenomenon termed *diffusion-driven instability*. Making the further assumption that cell fate was determined in a morphogen concentration-dependent manner, the chemical pre-pattern would manifest itself in a pattern composed of spatially heterogeneous cell fates.

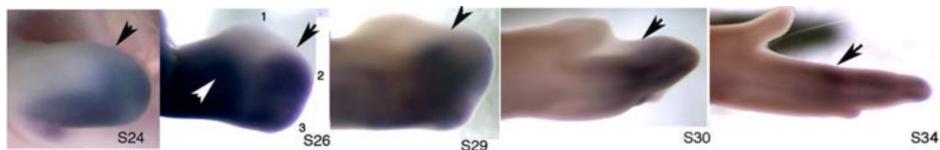
5.2.1 Diffusion Driven Instability

Consider a system of two morphogens (u, v) that are able to interact with each other through kinetics ($f(u, v), g(u, v)$) and diffuse throughout a one-dimensional domain, $[0, L]$, with diffusion coefficients (D_u, D_v) , respectively. Finally, we assume that the domain has zero-flux boundary conditions. The

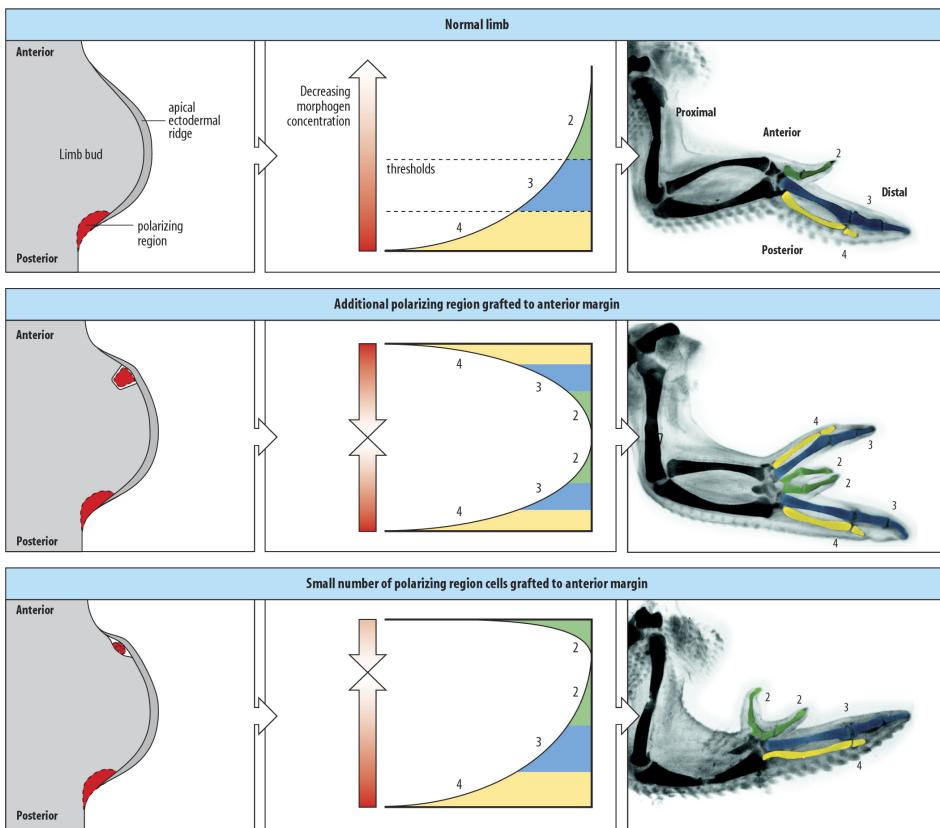
¹It is called Sonic Hedgehog because it was originally discovered in flies and upregulating the protein caused the flies to be covered with stiff hair spikes.



(a) A stage 26 chick foetus



(b) Forelimb bud developing digits.



(c) Control and altered digit development by adding exogenous Shh sources.

Figure 5.4: Digit development in chickens. See subcaptions for details. In (b) The arrows highlight Hox genes. The “S” numbers refer to the stage of development. You do not need to know these. Note each subcaption is a link to its source.

mathematical system representing this set up is

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u, v), \quad (5.13)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + g(u, v), \quad (5.14)$$

$$\frac{\partial u}{\partial x}(x, t) = 0 \text{ at } x = 0, L. \quad (5.15)$$

Definition 27. A homogeneous steady state, (u_s, v_s) , is a solution satisfying equations (5.13)-(5.15) assuming no spatial, or temporal, variation, i.e.

$$\frac{\partial u}{\partial t} = \frac{\partial v}{\partial t} = \frac{\partial^2 u}{\partial x^2} = \frac{\partial^2 v}{\partial x^2} = 0. \quad (5.16)$$

Using the above definition a homogeneous steady state satisfies

$$f(u_s, v_s) = 0 = g(u_s, v_s). \quad (5.17)$$

We will be looking for conditions under which these states evolve into patterns.

Definition 28. A diffusion driven instability, also referred to as a Turing instability, occurs when a homogeneous steady state, which is stable in the absence of diffusion, becomes unstable when diffusion is present.

The fact that diffusion is going to be responsible for the patterning we are considering is quite surprising. Diffusion, in isolation, disperses a pattern; yet diffusion, in combination with the kinetic terms, can drive a system towards a state with spatial structure.

5.2.1.1 A note on initial conditions

To fully close the system we need to specify initial conditions, $(u(x, 0), v(x, 0))$, however, these are unimportant and we will be simply assuming that they are random perturbations around the homogeneous steady state.

In a full simulation the final pattern will heavily rely on the initial conditions. Since we are assuming that there is no intelligence behind the pattern construction, these patterns are best suited to understanding individualised pattern, e.g. finger prints, zebra stripes, etc.

Equally, due to subcritical bifurcations of the patterning structures it could be possible for the initial conditions to dictate whether patterns are seen, or not. However, such subtleties outside of this course.

5.2.1.2 A note on boundary conditions

A homogeneous steady state requires the solution to be uniform across the entire domain. In other words the concentration profile will be flat, or

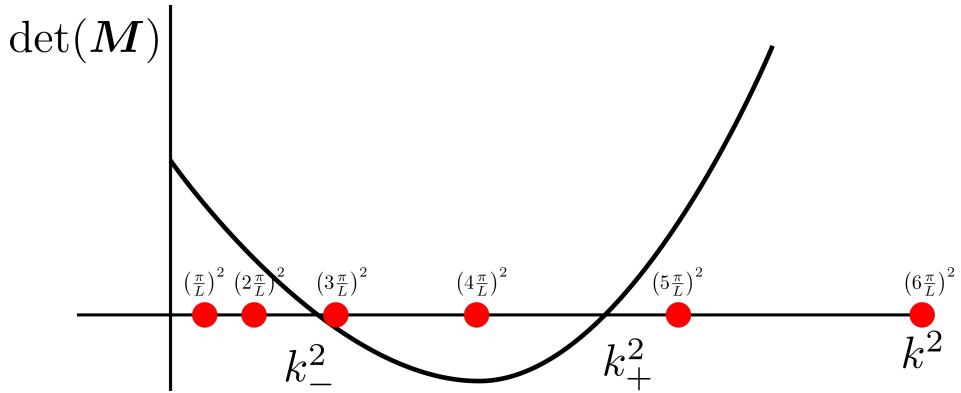
$$\frac{\partial u}{\partial x} = 0 = \frac{\partial v}{\partial x} \quad (5.18)$$

everywhere. We note that the homogenous Neumann boundary conditions easily satisfy such requirements. Alternatively, we could use Dirichlet boundary conditions, however, we could have to be careful as to how we fix the boundary values. Namely, we would require that the boundaries are compatible with the homogeneous steady states,

$$u(0, t) = u_s = u(L, t) \quad v(0, t) = v_s = v(L, t). \quad (5.19)$$

5.2.2 Stability without diffusion

5.2.3 Instability with diffusion

Figure 5.5: Schematic diagram of $\det(M)$.

Necessary conditions to produce patterning in using equations (5.13) and (5.14)

$$f_u + g_v < 0, \quad (5.45)$$

$$f_u g_v - f_v g_u > 0, \quad (5.46)$$

$$D_v f_u + D_u g_v > 0, \quad (5.47)$$

$$(D_v f_u + D_u g_v)^2 - 4D_u D_v (f_u g_v - g_u f_v) > 0, \quad (5.48)$$

$$\exists n \in \mathbb{Z} \text{ such that } k_- < \frac{n\pi}{L} < k_+. \quad (5.49)$$

5.2.4 Corollaries to Turing's theory

We have derived a number of necessary conditions that allow patterns to occur. However, considering our results a little further we gain a number of further insights.

Example 5.2.18 Specific Turing kinetic example: Schnakenberg kinetics

We consider a spatially extended version of the Schnakenberg kinetics as a model of morphogen populations,

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + \alpha - u + u^2 v, \quad (5.51)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + \beta - \alpha - u^2 v, \quad (5.52)$$

on a domain, $[0, L]$ with zero-flux boundary conditions and random perturbation around the steady state as an initial condition. Further, we suppose D_v, α and β are positive constants. Derive the Turing conditions that need to be satisfied for a pattern to appear.

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5.2.5 A comment on domain size and spatial dimensions

From the previous section we can conclude that as the one-dimensional domain gets larger (L increases) higher values of the integer n are valid in equation (5.48). Thus, we would expect that more peaks would appear as the domain gets larger. This is actually observed in nature (see figures 5.10(a) and 5.10(b)). However, animal coats are not one-dimensional, thus, we need to consider how our intuition generalises in higher dimensions.

Consider a Turing system on a two dimensional rectangle with $(x, y) \in [0, L_1] \times [0, L_2]$, zero flux boundary conditions and the Laplacian involving both second spatial derivatives,

$$\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}. \quad (5.83)$$

Our perturbation is then of the form

$$\begin{pmatrix} u \\ u_s \\ v_s \end{pmatrix} = \begin{pmatrix} u_s \\ v_s \end{pmatrix} + \begin{pmatrix} \epsilon_{u1} \\ \epsilon_{v1} \end{pmatrix} \cos(k_x x) \cos(k_y y). \quad (5.84)$$

Following the same procedure as above we find that the allowed values of k^2 are now

$$k^2 = k_x^2 + k_y^2 = \frac{m^2\pi^2}{L_1^2} + \frac{n^2\pi^2}{L_2^2}, \quad (5.85)$$

for some integers m and n , excluding the case where they are both zero.

Now, suppose the domain is long and thin, *i.e.* $L_2 \ll L_1$ and L_1 is sufficiently large. Then, since we require $k_- < k < k_+$, the only means by which we can have a Turing instability is if $n = 0$. Thus, the

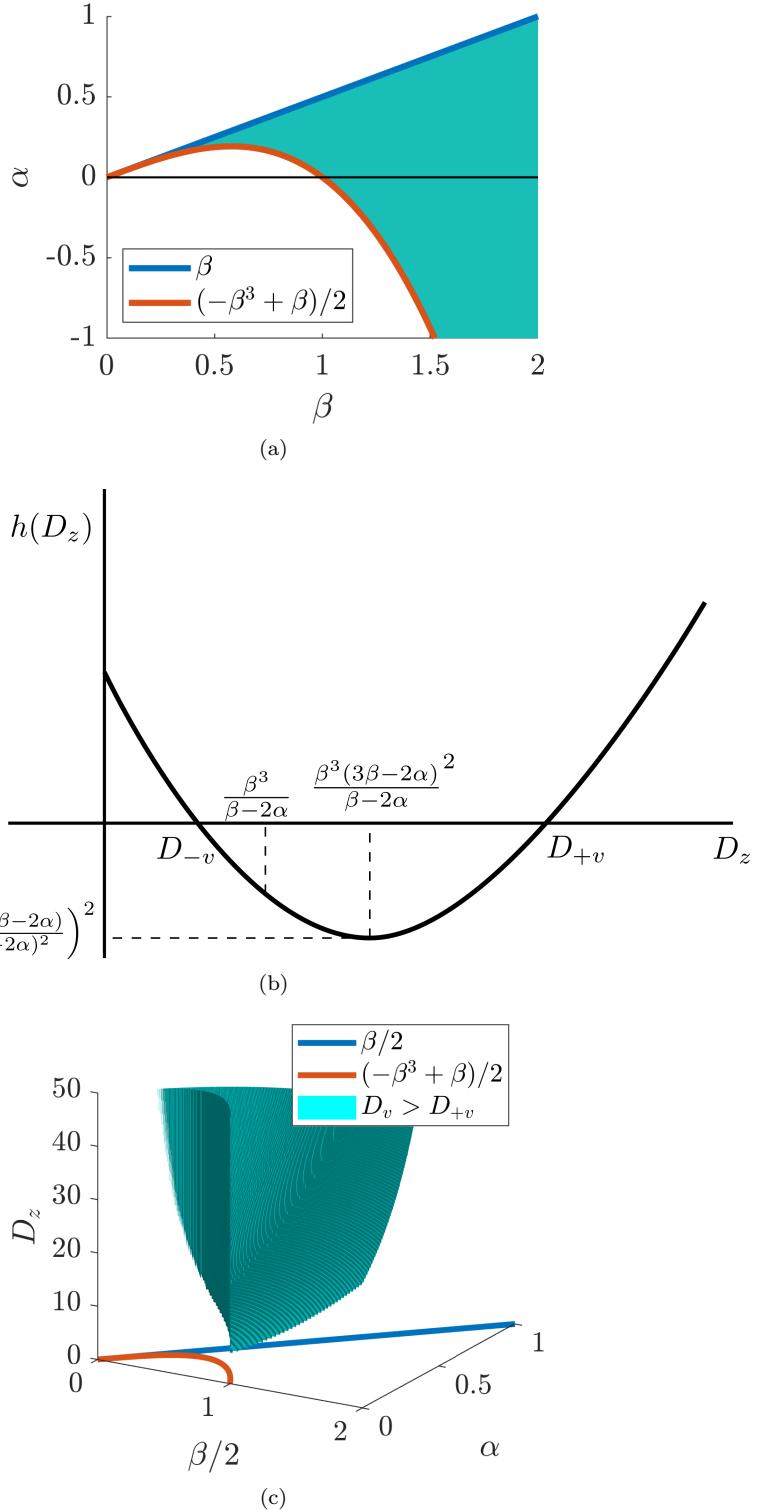


Figure 5.6: (a) (β, α) parameter region, which provides stable homogeneous steady states. (b) Schematic diagram of $h(D_v)$. (c) (β, α, D_v) parameter region, which provides diffusion driven unstable homogeneous steady states.

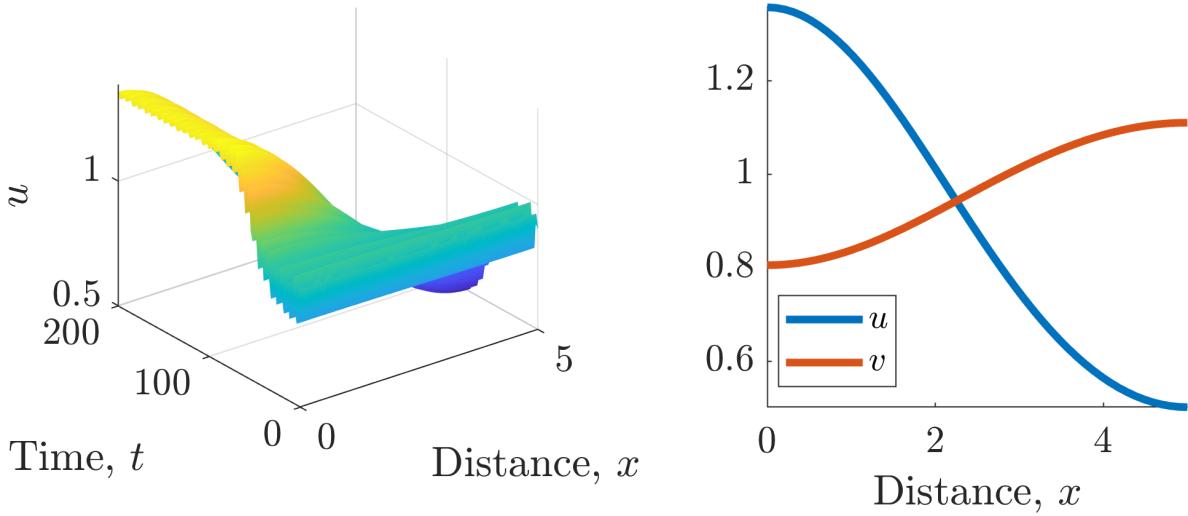


Figure 5.7: Simulation of equations (5.51) and (5.52) with parameters $(\alpha, \beta, D_v, L) = (0.1, 0.9, 10, 5)$. The left image shows the evolving concentration of u over space and time, whilst the right image shows the final heterogeneous solution.

linear analysis predicts that the patterns are going to be simply spatial oscillations in one dimension. In other words, the pattern will be striped.

For a sufficiently large rectangular domain, where $L_1 \approx L_2$, we can then satisfy the wave mode criteria with both n and $m > 0$. Thus, the linear analysis predicts spatial oscillations in both x and y directions. In other words, the pattern will tend to have a spotted structure (see Figure 5.8)

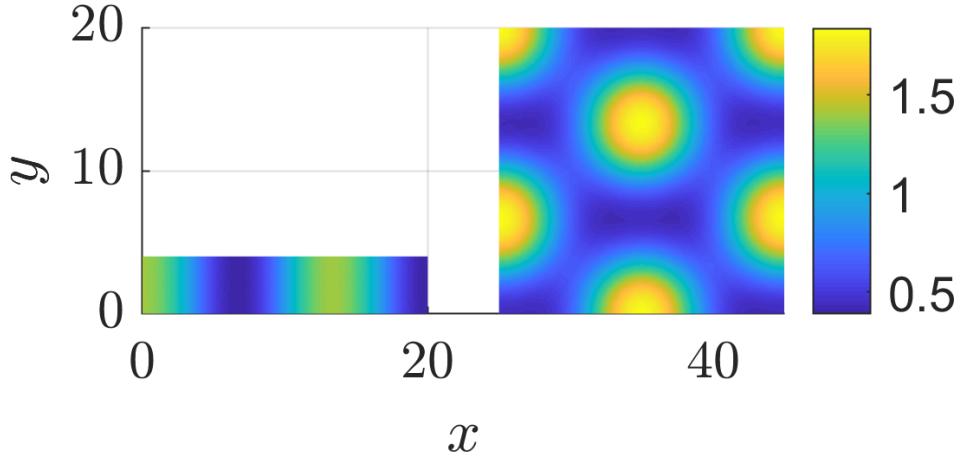


Figure 5.8: Simulation of equations (5.51) and (5.52) with parameters $(\alpha, \beta, D_v) = (0.1, 0.9, 10)$ on two different two-dimensional domain sizes.

Putting these insights together we see that as the patterning domain gets smaller the patterning type must transition in the following order: spots transform into stripes, which can transform into spatial heterogeneity (see Figure 5.9).

Thus, if Turing patterns are behind animal pigmentation patterns we should be able to see animals with spotty bodies and striped tails, but we would not expect to find an animal with a striped body and a spotted tail. Common observations are consistent with such a prediction (see Figure 5.10(c)) but one should not expect universal laws in the realms of biology, as one does in physics (see Figure

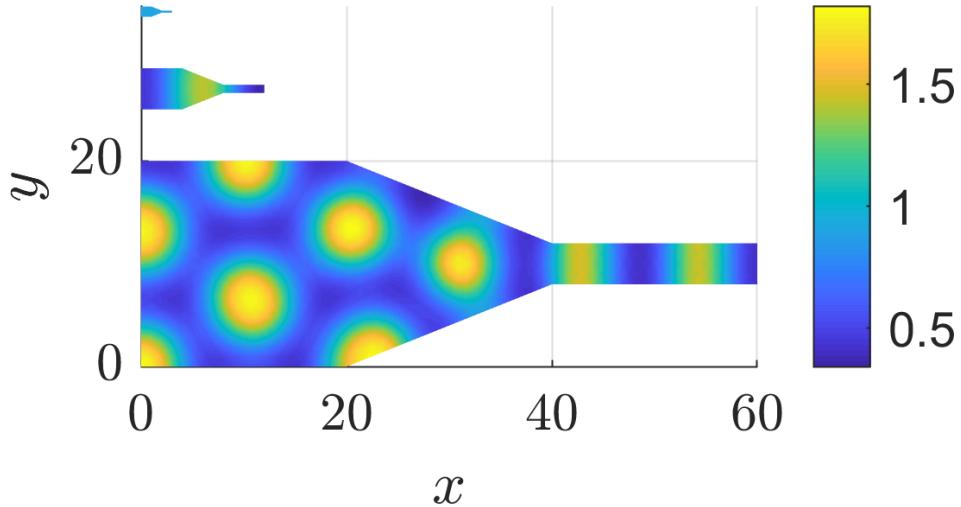


Figure 5.9: Simulation of equations (5.51) and (5.52) with parameters $(\alpha, \beta, D_v) = (0.1, 0.9, 10)$ on three sizes of tapered domain

5.10(d)).

5.3 Do they exist?

As we have seen, diffusion driven instabilities can theoretically drive pattern formation. Amazingly, there are lots of chemical systems where this is exactly the case (see Figure 5.11). Unfortunately, there is yet no conclusive evidence that it can drive pattern formation in biological systems. There are many suggestive pieces of work and many experimental labs are working on isolating the morphogens, but they are still only theoretical in biology.

Other groups have foregone looking for biological examples and are instead focused on creating their own biological systems that will generate the required conditions in a field called “synthetic biology”. They are generating a toolbox of biological components that can act like mathematical operators and, thus, they are essentially converting biological problems in computational problems.

We live in exciting times.

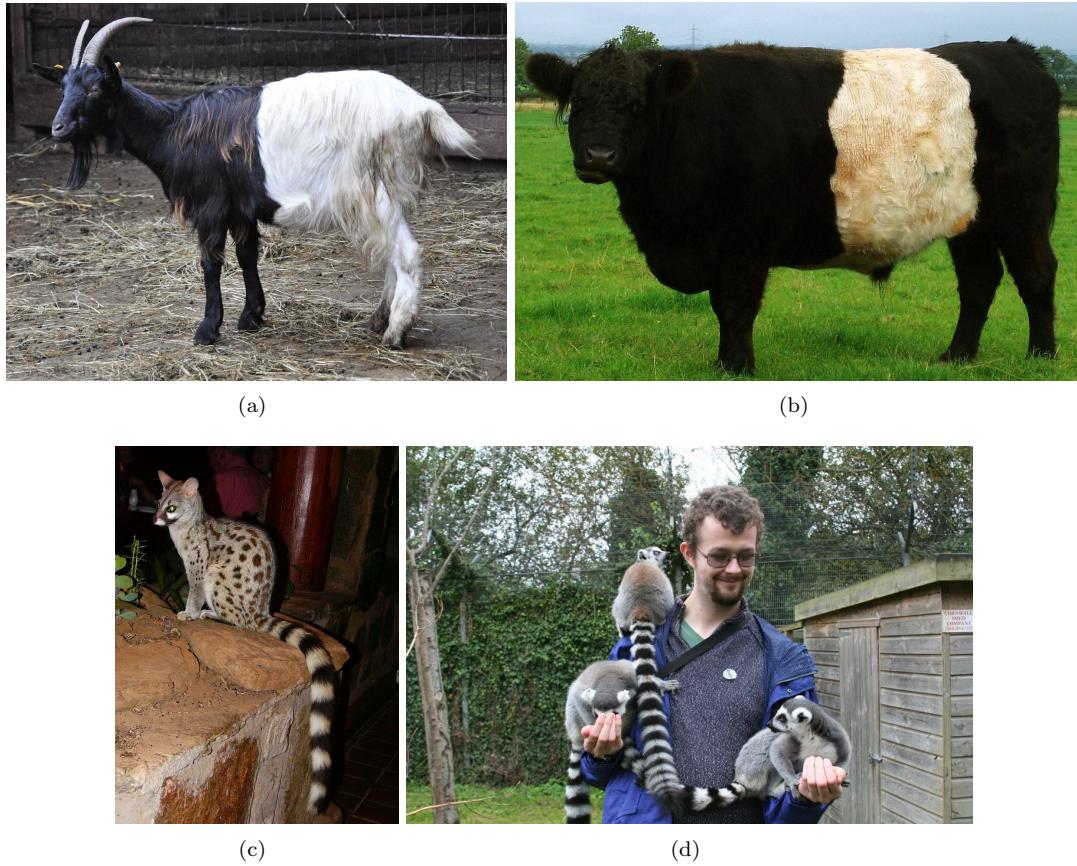
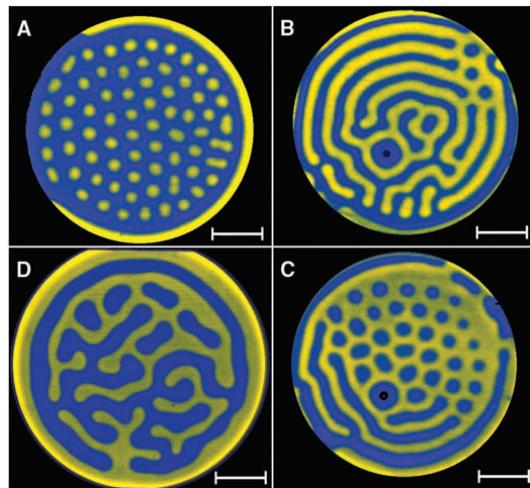
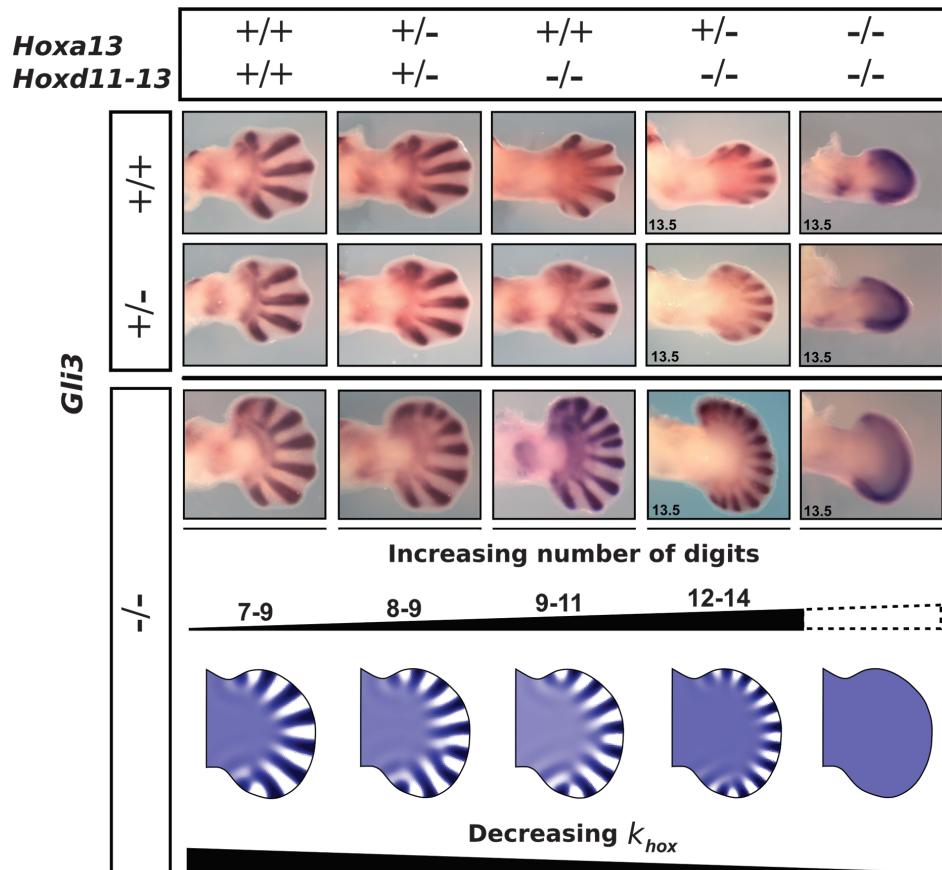


Figure 5.10: (a) Valais goats have one stripe transition whereas (b) Belted Galloways have two pigment transitions.(c) The genet cat has a spotted body and striped tail. (d) Lemurs have no pattern on the body and a striped tail.



(a) A chemically formed Turing pattern.



(b) Mouse limb development may be governed by a Turing-like patterning process.

Figure 5.11: Examples of pattern formation in chemistry and biology. Note each subcaption is a link to its source.

Appendix A

Proof of stability criterion for scalar ODE equations

Here we provide a proof of Theorem 2.5.1.

Proof. Consider a solution of the form $u(t) = u_s + \epsilon(t)$, where $|\epsilon(0)| \ll 1$. Substituting the perturbed solution into equation (2.22), we find that

$$\dot{\epsilon} = F(u_s + \epsilon). \quad (\text{A.1})$$

We now use Taylor's theorem on the right-hand side to derive the approximation

$$F(u_s + \epsilon) \approx F(u_s) + \epsilon \frac{dF}{du}(u_s) + \frac{\epsilon^2}{2} \frac{d^2F}{du^2}(u_s) + \dots \quad (\text{A.2})$$

Ignoring all terms except the linear order in ϵ we conclude that initially

$$\dot{\epsilon} \approx F(u_s) + \epsilon \frac{dF}{du}(u_s). \quad (\text{A.3})$$

By assumption u_s is a stationary point and, thus, by definition, $F(u_s) = 0$. Hence, approximately,

$$\dot{\epsilon} = \epsilon \frac{dF}{du}(u_s). \quad (\text{A.4})$$

Equation (A.4) is trivially solvable since $dF(u_s)/du$ is a constant,

$$\epsilon(t) = \epsilon(0) \exp\left(t \frac{dF}{du}(u_s)\right). \quad (\text{A.5})$$

The exponential solution form tells us that if $dF(u_s)/du < 0$ then $\epsilon(t) \rightarrow 0$ as $t \rightarrow \infty$. This means that our small perturbation dies out over time and the solution $u(t) \rightarrow u_s$ as $t \rightarrow \infty$. In other words u_s is stable because solutions that are slightly perturbed away from u_s tend to evolve back to u_s .

Oppositely, if $dF(u_s)/du > 0$ then $\epsilon(t) \rightarrow \infty$ as $t \rightarrow \infty$. Thus, the solution diverges away from u_s meaning that u_s is unstable. \square

Appendix B

Proof of stability criterion for ODE systems

Here we provide a proof of Theorem 2.5.2.

Proof. The proof follows exactly the same strategy as Theorem 2.5.1. Specifically, because differentiation is linear, you can use the exact same proof, but with tensors, rather than scalars. Namely, consider the perturbed solution $\mathbf{u}(t) = \mathbf{u}_s + \boldsymbol{\epsilon}(t)$, where $\|\boldsymbol{\epsilon}(0)\| \ll 1$. Substituting the perturbed solution into equation (2.29), we find that

$$\dot{\boldsymbol{\epsilon}} = \mathbf{F}(\mathbf{u}_s + \boldsymbol{\epsilon}). \quad (\text{B.1})$$

We now use a multi-variable form of Taylor's theorem on the right-hand side to derive the approximation

$$\dot{\boldsymbol{\epsilon}} \approx \mathbf{J}(\mathbf{u}_s)\boldsymbol{\epsilon}. \quad (\text{B.2})$$

To make progress, we assume \mathbf{J} is invertible, and, thus, diagonalisable. Critically, this means that we can find a complete set of eigenvectors, $\{\boldsymbol{\nu}_1, \dots, \boldsymbol{\nu}_n\}$, and eigenvalues, $\{\lambda_1, \dots, \lambda_n\}$, such that \mathbf{J} can be written as $\mathbf{J} = \mathbf{U}\mathbf{D}\mathbf{U}^{-1}$, where \mathbf{D} is a diagonal matrix with the eigenvalues along the diagonal, \mathbf{U} is a matrix with the, respective, eigenvectors as the columns and \mathbf{U}^{-1} is the inverse of \mathbf{U} . Substituting this form of \mathbf{J} into equation (B.2) produces

$$\dot{\boldsymbol{\epsilon}} = \mathbf{U}\mathbf{D}\mathbf{U}^{-1}\boldsymbol{\epsilon}, \quad (\text{B.3})$$

$$\implies \mathbf{U}^{-1}\dot{\boldsymbol{\epsilon}} = \mathbf{D}\mathbf{U}^{-1}\boldsymbol{\epsilon}. \quad (\text{B.4})$$

The matrix \mathbf{U}^{-1} is constant so we can take it within the time derivative on the left hand side. Hence, defining $\boldsymbol{\eta} = \mathbf{U}^{-1}\boldsymbol{\epsilon}$, we derive

$$\dot{\boldsymbol{\eta}} = \mathbf{D}\boldsymbol{\eta}. \quad (\text{B.5})$$

The closed form solution of equation (B.5) is

$$\boldsymbol{\eta} = \sum_{i=1}^n \mathbf{a}_i \exp(\lambda_i t), \quad (\text{B.6})$$

where \mathbf{a}_i are defined by the initial conditions. Thus, the stability of $\boldsymbol{\eta}$, and, hence, $\boldsymbol{\epsilon}$ depends on the eigenvalues, $\{\lambda_1, \dots, \lambda_n\}$ as stated in Theorem 2.5.2. \square

Appendix C

Characterising the stability of a two-dimensional ODE system

In the last Appendix we demonstrated that the stability of the steady states depends on the eigenvalues of the Jacobian. In this section, we restrict ourselves to considering two-dimensional systems only and illustrate that all steady states can be defined to fit a small number of categories.

The following derivation is going to be an explicit form of the proof shown in the last section. The reason for this is that the condensed vector form of proof is less transparent and it is always good to see a full sprawling derivation to illustrate the subtleties. Critically, although you may be specifically be required to reproduce the proof, in a specific case you can generally just calculate the Jacobian straight away and not bother with the initial linearisation steps.

Consider the general two-dimensional system

$$\dot{u} = f(u, v), \quad (C.1)$$

$$\dot{v} = g(u, v). \quad (C.2)$$

Let (u_s, v_s) , be a steady state, *i.e.* $f(u_s, v_s) = g(u_s, v_s) = 0$. Linearising around the steady state with $u = u_s + \epsilon_1$ and $v = v_s + \epsilon_2$ produces

$$\begin{aligned} \dot{\epsilon}_1 &= f(u_s + \epsilon_1, v_s + \epsilon_2), \\ &\approx \underbrace{f(u_s, v_s)}_{=0} + f_u(u_s, v_s)\epsilon_1 + f_v(u_s, v_s)\epsilon_2. \end{aligned} \quad (C.3)$$

and, similarly,

$$\dot{\epsilon}_2 = g_u(u_s, v_s)\epsilon_1 + g_v(u_s, v_s)\epsilon_2. \quad (C.4)$$

The eigenvalues will, thus, depend on the four parameters (f_u, f_v, g_u, g_v) . Note that we have not restricted the signs of these parameters. Thus, any of them could be positive or negative. Due to not knowing the signs of the derivatives we are unable to non-dimensionalise them out. However, in a specific example, this maybe possible, thus, reducing down the number of free parameter groups in the steady state and stability conditions.

Combining equations (C.3) and (C.4) we derive

$$\begin{pmatrix} \dot{\epsilon}_1 \\ \dot{\epsilon}_2 \end{pmatrix} = \begin{bmatrix} f_u & f_v \\ g_u & g_v \end{bmatrix} \begin{pmatrix} \epsilon_1 \\ \epsilon_2 \end{pmatrix}. \quad (C.5)$$

Thus, we are left to find the eigenvalues of

$$\mathbf{J} = \begin{bmatrix} f_u & f_v \\ g_u & g_v \end{bmatrix}, \quad (C.6)$$

namely

$$\det(\mathbf{J} - \lambda \mathbf{I}) = \begin{bmatrix} f_u - \lambda & f_v \\ g_u & g_v - \lambda \end{bmatrix},$$

$$= (f_u - \lambda)(g_v - \lambda) - f_v g_u,$$

$$= \lambda^2 - \lambda(g_v + f_u) + f_u g_v - f_v g_u, \quad (\text{C.7})$$

$$= \lambda^2 - \lambda T + D, \quad (\text{C.8})$$

where equations (C.7) and (C.8) are the same but equation (C.8) is rewritten in terms of the trace, ' $T = \text{tr}(\mathbf{J})$ ', and determinant, ' $D = \det(\mathbf{J})$ ', of the Jacobian, \mathbf{J} . Finally, the eigenvalues of \mathbf{J} have the form

$$\lambda_{\pm} = \frac{T \pm \sqrt{T^2 - 4D}}{2}. \quad (\text{C.9})$$

the stability of the steady states can now be characterised solely through the dependence of λ_{\pm} on T and D (see Figure C.1). Critically, although Figure C.1 is useful, it is suggested that instead of calculating the trace and determinant of the Jacobian and figuring out where in the stability diagram that you lie, you calculate the eigenvalues of any system explicitly.

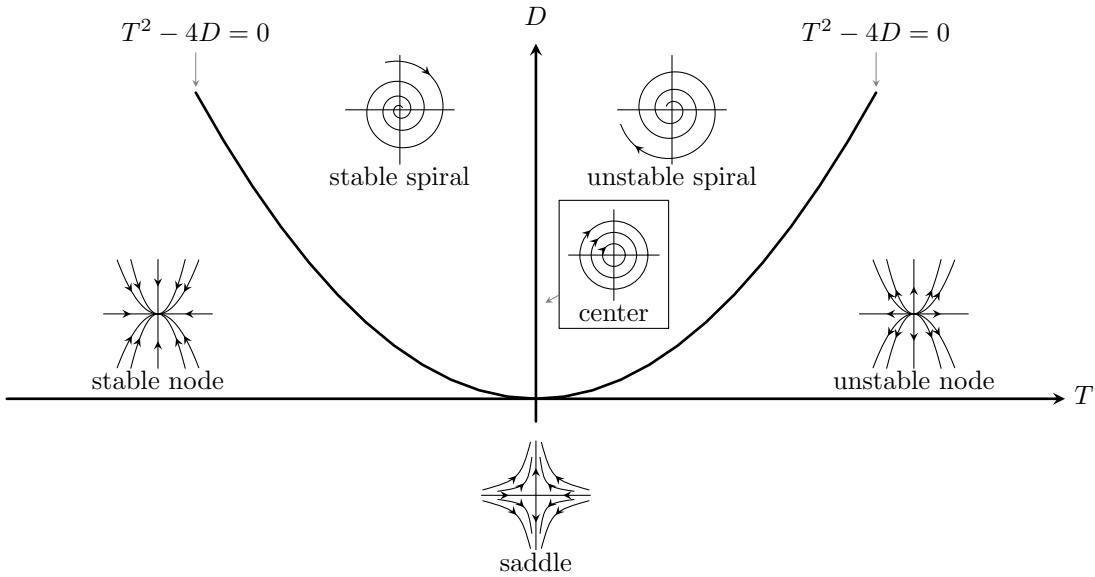


Figure C.1: Stability diagram in terms of the trace and determinant of the Jacobian.